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Table of Contents

Posters..................................................................................................................................................1

Aging/Alzheimer’s Disease (Abstracts in the 100s) ..................................................................................1
Biochemistry (Abstracts in the 200s).....................................................................................................12
Cancer (Abstracts in the 300s).............................................................................................................13
Cardiovascular (Abstracts in the 400s).................................................................................................42
Cell Biology (Abstracts in the 500s)....................................................................................................62
Community Medicine (Abstracts in the 600s).....................................................................................69
Diabetes (Abstracts in the 700s)...........................................................................................................75
Education (Abstracts in the 800s) .........................................................................................................85
Eye/Vision (Abstracts in the 900s)........................................................................................................91
General Medicine (Abstracts in the 1000s)........................................................................................102
General Public Health (Abstracts in the 1100s).................................................................................117
Health Disparities (Abstracts in the 1200s)......................................................................................150
Immunology (Abstracts in the 1300s).................................................................................................154
Integrative Physiology (Abstracts in the 1400s)..................................................................................156
Microbiology/Infectious Disease (Abstracts in the 1500s).................................................................167
Molecular Genetics (Abstracts in the 1600s)......................................................................................172
Neuroscience (Abstracts in the 1700s)................................................................................................174
Other (Abstracts in the 1800s)..........................................................................................................197
Pharmaceutical Sciences (Abstracts in the 1900s).............................................................................230
Pharmacology (Abstracts in the 2000s).............................................................................................234
Physical Medicine/OMM (Abstracts in the 2100s)..........................................................................238
Psychology (Abstracts in the 2200s)..................................................................................................243
Rehabilitative Sciences (Abstracts in the 2300s)..............................................................................251
Structural Anatomy (Abstracts in the 2400s)...................................................................................256
Women’s Health (Abstracts in the 2500s).......................................................................................268

Oral Presentations.................................................................................................................................281

Cancer (Abstracts in the 300s)...........................................................................................................281
Cardiovascular (Abstracts in the 400s).............................................................................................282
Immunology (Abstracts in the 1300s) ................................................................. 283
Integrative Physiology (Abstracts in the 1400s) ................................................... 285
Neuroscience (Abstracts in the 1700s) ................................................................. 286
Women’s Health (Abstracts in the 2500s) ......................................................... 289
Epigenetic Risk Factors for Mild Cognitive Impairment, Alzheimer’s Disease and Metabolic Dysfunction in Mexican Americans

Purpose: Alzheimer’s is the most common form of dementia and the 5th leading cause of death for those over 65\(^1\). The population of Mexican American elders will grow seven-fold by 2050\(^2\) with rates of mild cognitive decline (MCI) and Alzheimer’s disease (AD) increasing exponentially\(^1\). Mexican Americans are diagnosed with MCI and AD at younger ages than non-Hispanic whites\(^3\)\(^{-}4\). In addition, Mexican Americans who are diagnosed with AD are 1) less likely to carry the ApoE\(\varepsilon4\) genotype\(^3\)\(^{-}5\), 2) suffer a greater burden of type 2 diabetes\(^3\)\(^{-}6\), 3) experience greater metabolic-related cognitive decline\(^7\)\(^{-}8\) and 4) display a proteomic signature of AD that is heavily metabolic in nature\(^7\)\(^{-}9\), compared to non-Hispanic whites, whose proteomic signature for AD is dominated by inflammatory proteins. We hypothesized that differentially methylated regions of DNA (DMRs) are associated with age at onset of cognitive decline (MCI/AD) and metabolic dysfunction (metabolic syndrome/type 2 diabetes) in Mexican Americans.

Methods: To test this hypothesis, we assayed genomic DNA methylation in samples from 14 female Mexican American participants enrolled in the Health and Aging Brain study in Latino Elders (HABLE). Participants were diagnosed with cognitive decline (n=4), metabolic dysfunction (n=3), both (n=4), or as a control (n=3). We isolated DNA from leukocytes and bisulfite treated the samples before running them on an Illumina MethylFlash EPIC chip in accordance with manufacturer’s recommendations to assay genomic DNA methylation.

Results: Several interesting biological pathways showed significantly different methylation status between groups. When the participants were split on cognitive decline, DNA in the amyloid secretase, EGF receptor signaling, PDGF signaling, gonadotropin-releasing hormone receptor and Wnt-signaling pathways were significantly hypermethylated in cases. In comparison, analyses based on metabolic dysfunction showed significant DNA hypomethylation in the beta1 and beta2 adrenergic receptor signaling pathways and hypomethylation of the gonadotropin releasing hormone receptor pathway in cases.

Conclusions: The etiology of cognitive decline appears to differ between Mexican Americans and non-Hispanic whites. Future work will resolve how dementia risk differs between these and other ethnic groups. The knowledge gained from these studies will be critical to a better understanding of AD pathophysiology and the development of ethnicity-focused AD treatment options.
Acknowledgements: Research reported here was supported by the National Institute On Aging of the National Institutes of Health under Award Number R01AG054073. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The research team also thanks the local Fort Worth community and participants of the Health & Aging Brain Study.

**Sponsor:** R01AG054073  
**IRB/IACUC#:** 2012-083
Alzheimer’s and Automation: A Match Made in Research?

Objective:
Alzheimer’s is a disease that destroys memory, alters mental function, disrupts the autonomic nervous system and is detected only after an individual has had the disease for several years. Our research is dedicated to early detection of Alzheimer’s through blood-based biomarkers, clinical testing and MRIs. We are projected to see upwards of 3,000 people over a 5-year period. With one lab, four staff, and minimal sample process time, our research was in need of a system that could increase productivity, reduce human error and allow our samples to be fully processed from blood draw to freezer in under two hours. Our solution: the Hamilton Robotics Easyblood robot combined with a customized LIMS system.

Methods:
The lab was in need of a system to fully capture the blood collection process. To capture this information, a LIMS system was developed to document each milestone the sample reached such as time of blood draw, time into centrifuge, etc. The Easyblood robot was programmed to aliquot blood fractions (GLP-1 plasma, plasma, buffy coat and serum) to fit our needs based on each project’s protocol. For the LIMS system and Easyblood robot to communicate with each other, an SQL server database was utilized to link the LIMS system to Easyblood through a developed common bond: barcoded collection kits. Each collection kit (EDTA, SST, and p800 tube) has a project barcode and each tube in the collection kit has its own barcode, denoted by sample type.

Results:
With the implementation of the Easyblood robot and the LIMS system, the lab is able to track the blood collection process from beginning to end. This information enables lab personnel to process multiple samples at one time, easily identify the samples, reduce the amount of time between collection and storage and minimize human error.

Conclusion:
The two systems working in conjunction with each other allows for increased consistency, simplicity, and reliability in processing blood-based samples.

IBC # 2017-0056
Sponsor: N/A
IRB/IACUC#: 2015-171
Tissue-specific effects of Exercise and Antioxidant Intake on Protein Damage in Young and Old Mice

1. Purpose:
While oxidative stress is not the only factor involved in the aging process, it has been demonstrated that manipulating oxidative stress can affect function and delay age-related declines. Interventions such as moderate exercise and antioxidant supplementation have been shown to affect oxidative stress and improve function. With many individuals combining interventions, it is imperative to determine how they might interact. We hypothesized that exercise or antioxidants alone would decrease oxidative damage, and combining them would further decrease oxidative damage.

2. Methods:
Cardiac and skeletal muscle tissues were homogenized and used to determine the levels of protein damage assessed by measuring carbonyl concentrations. The samples were collected from a prior study during which 4 and 20 month old C57BL/6 male mice were placed into one of four treatment groups: sedentary/ control diet, sedentary/ antioxidant diet, exercise/ control diet, and exercise/ antioxidant diet. The exercise consisted of a moderate aerobic treadmill forced exercise, and the antioxidant diet contained α-tocopherol (0.825mg/g diet) and ascorbate (1.65mg/g diet). The effects of age and treatment were analyzed by two-way ANOVAs, followed by pairwise comparisons.

3. Results:
There was no main effect of age on protein oxidation in homogenates from cardiac or skeletal muscles. There was no effect of exercise, antioxidant or the combination on carbonyls in the skeletal muscles. However, in the cardiac muscles, all the treatments decreased protein oxidation especially in the old mice (only significantly in the old exercise group). There was no noticeable interaction between antioxidant and exercise treatments.

4. Conclusion:
Overall, the effects of treatment were only observed in the cardiac muscle signifying a potential tissue-dependent response to exercise and antioxidants. Interestingly, there was no beneficial or antagonistic interaction between the two interventions. Other tissues will also be studied to strengthen this argument.

Sponsor: T32AG020494 (NIH/NIA), 5R25HL007786-25 (NIH/NHLBI)
IRB/IACUC#: N/A
The Effect of Hearing Aids on Balance

Purpose: Older adults with hearing loss fall more often compared to older adults with normal hearing. Although some clinical balance outcome measures have been identified as potential assessment tools for older adults with hearing loss who are risk for falling, no study has assessed reactive balance outcome measures for older adults with hearing loss to determine fall risk. This study assessed whether number of steps during loss of balance, while simultaneously listening and responding to a standardized audiology test, could be a feasible reactive balance outcome measure to use to identify older adults with hearing loss who have balance deficits.

Methods: 20 young adults, 20 older adults with normal hearing, and 20 older adults with hearing loss performed an auditory-balance dual-task of listening to a standardized audiology test, the BKB-SIN, while simultaneously responding to forward loss of balance requiring participants to take a step. Backward surface translations were provided on a treadmill at a slow and fast speed and randomized with the auditory sentences.

Results: Results showed no significant difference between young adults, older adults with normal hearing, and older adults with hearing loss on balance or auditory scores.

Conclusions: Further research needs to be performed to identify proper assessments and treatment interventions for older adults with hearing loss who have balance deficits.

Sponsor: NIH Neurobiology of Aging grant - T32 020494
IRB/IACUC#: 2016-099
Testosterone in the bedroom - not always good

Purpose: There are no effective therapeutics to prevent the progression of neurodegenerative diseases, such as Alzheimer’s disease (AD) or Parkinson’s disease (PD). This deficit highlights the need to identify early contributors to neurodegenerative pathophysiology, such as examining common comorbidities. One such comorbidity is sleep apnea. To examine the relationship between sleep apnea and neurodegeneration, we used a rodent model of chronic intermittent hypoxia (CIH) to simulate the hypoxic events experienced by patients with sleep apnea. Interestingly, in male rats CIH causes an increase in oxidative stress (OS) and inflammation, along with a decrease in circulating testosterone (T). Currently, studies have been equivocal about the role of the major male sex hormone, T, in neuroprotection and neurodegeneration. It has been proposed that an OS environment may predispose T to be neurotoxic via androgen receptor activation.

Methods: To address if OS is the switch for testosterone’s neuroprotective or neurotoxic actions, male Long-Evans rats were assigned to different hormone groups: gonadally intact, gonadectomized (GDX), GDX + T (TRT) or GDX + dihydrotestosterone (DHT). DHT is an androgen receptor agonist metabolized from T. Two weeks after hormone replacement, rats were exposed to CIH or room air (AHI = 8) for 12 days. During the last 5 days of CIH, cognitive and motor behavioral tests were conducted.

Results: As expected, elevated OS as well as spatial memory and fine motor impairments were observed in response to CIH in gonadally intact rats. This suggests CIH-induced OS results in behavioral deficits associated with early-stages of neurodegenerative diseases. GDX rats exhibited only cognitive impairments, regardless of CIH exposure, indicating sex hormones play a role in memory. Irrespective of CIH exposure, TRT prevented OS generation as well as motor and cognitive impairments. Interestingly, CIH induced OS and cognitive impairments were exacerbated in DHT male rats, compared to gonadally intact rats.

Conclusions: These results indicate that the androgen receptor is involved in T’s negative effects in an OS environment. Since sleep apnea is a common comorbidity of neurodegeneration, the observed sex differences may be due to a negative interaction between OS and androgen receptor activation. Therefore, men with sleep apnea who have elevated OS may be susceptible to neurodegenerative pathophysiology.

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IRB/IACUC#: 2014/15-50-A05
Potential Mechanisms by which Chronic Benzodiazepine Promotes Motoric Aging in Mice

PURPOSE

Benzodiazepines (BZDs) are among the most commonly prescribed medications in elderly to treat hyperexcitatory disorders such as anxiety and insomnia. However, its high or a repeated dose is frequently administered to patients, which often provokes side effects including motoric impairment. Here, we investigated whether chronic BZD (lorazepam) age-dependently deteriorates motoric functions in mice.

METHODS

To decipher underlying mechanisms, we measured mitochondrial BZD-receptor (mBZD-R) and amyloid-β (Aβ) of which excess amount is associated with mitochondrial deficit and neurodegeneration. We also measured reactive oxygen species (ROS) and cell survival in HT22 cells, the cell line that has been used to determine oxidative mechanisms. Young (3 months old) and old (15 months old) mice received BZD (lorazepam, 1 mg/kg) with or without mBZD-R inhibitor (PK11195) for 4 weeks. Motoric function was tested using Rotarod; a quicker fall from rotating rod indicates a poorer motoric function. Upon humane sacrifice, cerebellum was collected to measure mBZD-R using immunoblot and amyloid-β using sandwich ELISA. Separately, HT22 cells were treated with lorazepam (0-25 µM) for 3 days. The cells were then tested for mitochondrial ROS, whole cell ROS, and cell viability using MitoSox, DCFDA, and Calcein assays, respectively.

RESULTS

BZD-received old mice showed poorer motoric function, increased mBZD-R, and Aβ accumulation in cerebellum more severely than old control or young-BZD mice. PK11195 injection tended to improve the motoric function of BZD mice. Chronic BZD treatment to HT22 cells showed an increase in mitochondrial ROS in a manner attenuated by PK11195 treatment and accompanied by reduced cell survival.

CONCLUSIONS

These data suggest that chronic BZD exacerbates the motoric deterioration in aged mice. These data also raise a possibility that a deleterious interaction between mBZD-R and mitochondrial ROS is a part of the underlying mechanistic network responsible for the motoric aging.

Sponsor: N/A
IRB/IACUC#: 2016-0035
Predictors of estrogen’s neuroprotective efficacy

Purpose:

The precipitous decline in ovarian hormones after the menopause may put women at greater risk for age-associated cognitive decline and serves as the basis for considering hormone therapy to support brain health, despite equivocal results in clinical trials studies to-date.

Data from our lab show that estrogen replacement (after ovariectomy) in young animals increases brain-derived neurotrophic factor (BDNF) mRNA expression in the hippocampus. However, in middle-aged animals, the effect of 17b-estradiol (E2) is diminished, supporting the existence of a window of opportunity for these hormones, and thus, reason to explore the underlying molecular mechanisms.

In this study, we evaluated the expression of BDNF, estrogen receptors (ERs), and other relevant molecules of cognition (TrkB, p75, and RbAp48) in young and middle-aged animals to determine if changes in their expression was correlated with the effect of estrogen. To better establish any causal relationship to our findings, we also conducted studies in vitro to determine which ERs are critical to mediating the effects of E2 on BDNF.

Methods:

*In-Vivo:* Real time rtPCR was used to evaluate the expression of BDNF, TrkB, p75, RbAp48, and ERα mRNA in the hippocampus of female ovariectomized (OVX) Sprague Dawley rats that were 4 months (young) and 10 months (middle-aged) of age.

*In-Vitro:* The effect of E2 (10nM, 24 hours) on BDNF mRNA expression was evaluated in ERα transfected, differentiated SH-SY5Y cells (as a model of ER negative neurons). In parallel, we also evaluated the effect of E2 on cell viability (using the MTT assay).

Results:

Our *in vivo* data show that ERα, BDNF, TrkB, RbAp48 in hippocampal mRNA are significantly decreased in middle-aged OVX rats as compared to young OVX. There was also a significant increase in the pro-cell death p75 receptor in middle-aged rats. *In vitro* data revealed a significant increase in ERα mRNA expression post-transfection, with an approximate 30% transfection efficiency. Treatment of ERα-transfected SH-SY5Y cells with E2 did not induce a significant increase in BDNF, nor did it protect the cells from amyloid-beta-induced cytotoxicity.

Conclusion:

The hippocampal mRNA expression analyses we performed *in vivo* suggest that indeed, there are changes in relevant molecules of cognitive function with age, that in turn, could diminish the protective
effects of E2. Further, ERa expression was not sufficient to mediate the effect of E2 on BDNF expression or cell viability.

Sponsor: Funding for this work was supported in part by AG022550, AG027956, and T32 AG020494. IRB/IACUC#: 2014 15-49
The relationship of Hypertension and related Cardiovascular Risk factors to Executive Functioning in Mexican-Americans

Background: The effect of high blood pressure on cognitive domains is unclear but the literature suggests that the primary impact is on cognitive impairment in executive functions and slowing of mental processing speed. These cognitive functions are especially vulnerable to vascular change. Hispanics are at increased risk for cardiovascular disease, cognitive decline and dementias, and there is no sufficient literature about this relationship in this growing segment of the population. The purpose of this study was to examine the link between blood pressure and executive functioning in Mexican-Americans.

Methods: Data were analyzed in 426 participants from the Health and Aging Brain Among Latino Elders study (HABLE). Cardiovascular disease (CVD) risks include hypertension, dyslipidemia, diabetes mellitus, and abdominal circumference over 40 inches. The presence of these risks was determined from self-report, use of medication, and lab results. Trails B was used as an index of executive function and entered as the dependent variable in the models. A one-way ANOVA was conducted to assess the effect of CVD risk factors on executive function. Linear regressions were utilized to examine the relationship between hypertension and other CVD risk factors with executive function. Age was entered as a covariate in the model.

Results: Within the total sample, ANOVA revealed a statistically significance difference between groups (F (4,495) = 3.15, p = .01). The post hoc tests showed that the individuals with two (M = 7.7, SD = 3.7), three (M = 7.4, SD = 3.9) or four (M = 6.9, SD = 3.6) risk factors differ significantly at p < .05, with the zero (M = 9.6, SD = 3.6) and one (M = 8.0, SD = 3.5) risk factors groups. Diagnosis of hypertension significantly predicted Trails B scores ($b = -1.6$, 95% CI [-2.36, -0.80], $p = .00$). Hypertension explained a 4% of variance in Trails B scores, ($R^2 = .04$, $F (1,398) = 15.78$, $p = .00$). None of the other CVD risk were significant.

Conclusion: Our findings suggested a relationship between diagnosis of hypertension and executive function in Mexican-Americans. No other CVD risk factors independently had a significant link with executive function. Having more than one CVD risks regardless of its nature was related to lower executive functioning. The results of this study support literature that suggested that the effects of high blood pressure on cognitive domains primarily involve executive functioning.

Sponsor: N/A
IRB/IACUC#: 2012-083
Incorporating health literacy principles into student’s curriculum will improve confidence and overall ability to effectively communicate with older adults

Purpose: Adults over age 65 are at a higher risk for low health literacy. According to a survey from the National Assessment of Adult Literacy (NAAL), more than half of seniors (59%) have below basic literacy levels. In order to combat this issue, educating health professional students on health literacy strategies can increase the understanding of such disparities, and enhance communication capabilities with seniors.

Methods: Students encompassing seven health professions between two universities (n=620) were assembled into interprofessional teams and assigned a senior mentor (n=171). The teams were asked to develop a presentation covering a designated health topic of their mentor’s choice using health literacy principles. Following the presentation, a sampling of the senior mentors (n=75) and all of the students involved were surveyed and results were evaluated for effectiveness. Among the older adults and students, the response rate was 91% and 75% respectively.

Results: According to students surveyed, 70% agreed that as a result of this visit, they now understand how to effectively communicate with older adults using health literacy strategies. Seventy-four percent of students also felt more confident about their knowledge of health care needs for older adults. When reviewing senior mentor responses, 98% said after the presentation, they feel better informed on the given subject. Additionally, 85% were able to recall two pieces of information learned, and 98% feel they will be able to apply what they learned from the presentation to their health. When estimating if any change had occurred because of the presentation, 98% of seniors said they experienced some amount of positive change.

Conclusions: Application of health literacy strategies within interprofessional healthcare teams can have a positive effect on future communication and confidence when discussing health matters with older adults.

Sponsor: N/A
IRB/IACUC#: 2009-074
Computational Insights into Cas9 Conformational Activation and Specificity Enhancement

Over the past a few years, the biotechnology harnessing the microbial CRISPR/Cas systems has revolutionized the field of genome editing. The RNA-guided endonuclease Cas9 from *Streptococcus pyogenes* (SpCas9) can be programmed with a synthetic single guide RNA (sgRNA) to induce site-specific double-stranded DNA (dsDNA) cleavage. Despite recent progresses in deciphering the Cas9 structural and functional mechanisms, the knowledge of the Cas9 HNH nuclease domain catalytic state remains sparse, and it remains elusive as to how the catalytic Mg$^{2+}$ affects the HNH domain conformational transition. A deeper understanding of Cas9 conformational activation and its action mechanism is of fundamental importance for guiding the improvement of Cas9-mediated genome-editing specificity and efficiency. Herein we report a cross-validated catalytic state of the Cas9 HNH domain poised for cutting the target DNA strand by means of two distinct molecular dynamics (MD) simulation strategies. We note that the derived model has been in good agreement and rationalized by various available experiments. Moreover, we demonstrate the essential roles of Mg$^{2+}$ for the cleavage-state formation and stability. Importantly, our study suggests additional promising mutation sites on Cas9 that could be exploited for rationally engineering more Cas9 variants with enhanced specificity.

**Sponsor:** N/A

**IRB/IACUC#:** N/A
Combination of Mithramycin and Standard Chemotherapeutic Agents Induces Anti-proliferative activity in Ewing Sarcoma cell lines

Background/Hypothesis:
Ewing sarcoma (ES) is a small, round, blue cell tumor found primarily in bones of adolescents. The EWS-FL1 transcription factor is associated with proliferation of cancer cells and is over-expressed in >85% of Ewing sarcoma cases. Mithramycin (MIT) is an antibiotic with antineoplastic properties and has been shown to inhibit EWS-FL1. A recent trial of MIT treatment in ES patients found that hepatotoxicity precluded the administration of MIT at a dose required to inhibit EWS-FL1 (>50nmol/L). We hypothesize that the efficacy of adjunct treatment can be enhanced if MIT is used along with standard chemotherapeutic agents such as Vincristine (VIN) and Etoposide (ETO). Combination treatment will reduce the effective dose of both Mithramycin and the standard agent thereby decreasing the therapeutic dose range and side effects.

Methods:
ES cells, CHLA10 and TC205 were cultured in the presence of vehicle or MIT or VIN or ETO or in combinations (MIT+VIN or MIT+ETO). After 2 days, cell viability was measured using The CellTiter-Glo® Luminescent Cell Viability Assay kit. The apoptosis induced by each of the above-mentioned treatments on the ES cells was measured by Flow cytometry using Annexin V Apoptosis Detection Kit. The expression of cleaved-Poly (ADP-ribose) polymerase (c-PARP), a marker for apoptosis was determined by Western blot analysis.

Results:
While all treatments showed ES cell growth inhibition, the combination treatment of MIT+ETO was more effective (significant at p)

Conclusion:
The combination MIT+ETO caused more cell growth inhibition when compared to individual treatments in the TC205 and CHLA10 cell lines. These results demonstrate that MIT in combination with standard chemotherapeutic agents potentially increases therapeutic efficacy in ES. However, these results are limited to in vitro studies and need to be tested in an animal model to determine reproducibility and assess the toxicity.
**Sponsor:** HyundaiHopeOnWheels Young Investigator Award and TCOM Honors Research Practicum

**IRB/IACUC#:** CCHCS-IRB
Copper Tolfenamic acid induces anti-proliferative activity effective against Medulloblastoma cells

Purpose: Medulloblastoma (MB) is the most common pediatric malignant brain tumor, comprising 20% of all childhood brain tumors. Between 250-500 children per year are diagnosed in the US alone. Standard therapies result in severe long-term morbidities. Therefore, there is an urgent need for inventing novel effective treatment strategies with lower side-effects. Our laboratory showed anti-cancer activity of Tolfenamic acid (TA) in pre-clinical model for MB. Recent studies showed higher pharmacological effect of TA when synthesized as a complex with copper (Copper-TA, Cu-TA). Our aim was to investigate the anti-cancer activity of Cu-TA against MB cell lines. We hypothesize that Cu-TA presents higher anti-cancer activity and is more effective than TA to induce cytotoxicity against MB cells.

Methods: DAOY and D283 cells were obtained from ATCC and grown following standard cell culture conditions. Cells were treated with TA or Cu-TA and the cell viability was measured at 24 and 48 h post-treatment using a CellTiter-Glo kit. The induction of apoptosis was investigated by studying caspase activation using the Caspase 3/7-Glo kit. In addition, reactive oxygen species (ROS) involvement was measured by flow cytometry.

Results: Both Cu-TA and TA treatment resulted in decreased cell viability. However, when compared to TA, Cu-TA was more effective at inducing anti-proliferative activity in MB cells. Cu-TA induces increased production of ROS. The anti-proliferative activity of Cu-TA was accompanied by an increase in Caspase 3/7 activity, suggesting the induction of apoptosis.

Conclusions: Cu-TA was more effective than TA. Therefore, it has potential as an effective anti-cancer agent for inhibiting MB cell growth. Further studies are needed to better understand Cu-TA’s mechanism of action.

Sponsor: N/A
IRB/IACUC#: N/A
Sympathetic Chain Schwannoma Masquerading as a Vagus Nerve Schwannoma Complicated by Postoperative Horner’s Syndrome and Facial Neuralgia: A Case Report

Background: Schwannomas of the carotid sheath are rare neoplasms and schwannomas of the cervical sympathetic chain are the least common subtype. Despite predictive radiologic patterns, Cervical sympathetic chain schwannomas (CSCS) have been known to masquerade as other neoplasms on CT and MRI making preoperative diagnosis difficult. Postoperative complications are common. We present a rare case of a misdiagnosed CSCS with unusual complications of permanent Horner’s syndrome and facial neuralgia.

Case Information: A 36-year-old female presented with a right neck mass. CT and MRI confirmed the mass in the parapharyngeal space. The positioning of the mass in conjunction with the common carotid artery and the internal jugular vein lead to a diagnosis of vagus nerve schwannoma (VNS). During surgical treatment, dissection to the mass revealed the preoperative diagnosis of VNS to be incorrect as the mass was found to be involved with the cervical sympathetic chain. A new diagnosis of CSCS was made and the nerve was enucleated along with the mass. The patient presented postoperatively with Horner’s syndrome and severe facial neuralgia. Despite maximal medical management for two years, these complications have proved permanent.

Conclusions: Imaging is the mainstay for preoperative diagnosis of CSCS. While imaging trends allowing distinction between VNS, CSCS, and other tumors are helpful, recent studies have shown considerable variability in these trends making preoperative diagnosis difficult. Our case reflects this difficulty as preoperative imaging led to an incorrect diagnosis. In addition, post-operative complications, such as temporary Horner’s syndrome are common in CSCS. The patient in our case presented with more severe and unique complications of facial neuralgia and permanent Horner’s syndrome. These complications are not often seen in the literature. Future research should be undertaken to determine if a link between an incorrect preoperative diagnosis and an increased complication rate exists. In addition, this case serves to heighten clinician consciousness of a rare but important diagnosis and the difficulties involved with initial diagnosis and potential complications. We hope that such knowledge will prompt physicians to prepare thoroughly for possibly alternative diagnoses during surgical intervention which may lead to improved patient outcomes.

Sponsor: N/A
IRB/IACUC#: 2018-023
A Literature Review of Exercise in the Pediatric Oncology Population

The advances in treatment of children with cancer have been improved in recent years. This has resulted in an increase in the number of pediatric cancer survivors. Several research studies have shown that the medical condition and its related disorders is associated with impaired growth and development, decreased strength, fatigue, cognitive dysfunction, cardiopulmonary compromise, impaired physical fitness, musculoskeletal complications and decreased quality of life. There is growing evidence that lack of participation in physical activity in children with disability including children with pediatric oncology may result in several negative effects and decrease quality of life. In recent years, several exercise programs have been implemented for pediatric oncology.

Purpose

The purpose of this literature review is to examine evidence regarding the potential benefits of exercise for children with pediatric oncology. Safety, benefits, and application are addressed.

Methods

This systematic review identified 18 articles that met our inclusion criteria. Electronic databases used were PubMed, Physiotherapy Evidence Database (PEDro), CINAHL, Rehabilitation Oncology Journal, and Scopus. Key words included pediatric, children, oncology, exercise, and rehabilitation. Our initial search yielded 271 potential articles, which we screened for selection criteria. In total, 751 children with cancer were studied in our final research articles.

Results

In total, 18 research studies were examined and met our inclusion criteria for aerobic exercise in pediatric oncology patients. Of the included articles, 12 were randomized controlled trials, 2 were quasi-experimental design, 3 were cohort studies, and 1 were clinical trial. Across all 18 studies, 751 children with pediatric oncology were participants. Sample size for each study ranged between 7 and 150 children. All studies showed beneficial effects of exercise training for children with pediatric cancer.

Discussion and Conclusion

This systematic review adds to the body of literature that supports exercise training for individuals with pediatric oncology. Studies included support the beneficial effects of exercises for children with cancer. Further studies are needed to determine long term effects of any intervention. Available literature on exercise in children with pediatric oncology suggests that there are beneficial effects without adverse outcomes.

Sponsor: N/A
IRB/IACUC#: N/A
Prevalence and Risk Factors for Malnutrition during Pediatric Acute Lymphoblastic Leukemia Induction Therapy

Purpose

It is well documented that pediatric patients with acute lymphoblastic leukemia (ALL) often experience significant weight gain during induction therapy and later struggle with obesity. However, some patients experience unintended weight loss during induction therapy; since this issue is not well reported, it often goes unnoticed or undertreated.

Although malnutrition is reported to be associated with decreased survival, increased risk of infection and loss of lean body mass, there remains a scarcity of in depth analysis of prevalence and risk factors that contribute to this problem. Our study attempts to address this critical yet unmet need.

Our aim was to identify the clinical risk factors and outcomes associated with weight loss during induction therapy for pediatric ALL.

Design/Method

This was a retrospective chart review of patients between 2 and 20 years of age diagnosed with ALL at Cook Children’s Medical Center from 4/1/14 to 3/31/17. For each patient, we collected height, weight, age, body mass index (BMI) z-scores at diagnosis and end of induction therapy, risk stratification, and whether consolidation was delayed. Patients with a BMI z-score >85th percentile at diagnosis were categorized as being overweight or obese. Using logistic regression analyses, we examined which variables predicted whether the patient had an increase or decrease in BMI z-score throughout induction. A critical alpha level of 0.05 indicated statistical significance.

Results

Ninety-six patients met our inclusion criteria. Of these, 40% experienced a decrease in BMI during induction therapy. Compared to patients whose BMI increased during induction, patients with a decrease in BMI were more likely to be overweight or obese at diagnosis (55% vs. 22%; p

Conclusion

This research highlights a risk not previously identified in the literature that may impact outcomes. Patients treated on high- or very-high-risk protocols, who are overweight or obese at diagnosis, and who are ≥10 years old at diagnosis should be monitored closely for weight loss during induction therapy. Patients who experience weight loss should receive prompt intervention. It is our hope that this information can be used for future prospective studies and help develop evidence-based guidelines.

Sponsor: CCHMC

IRB/IACUC#: CCHCS-IRB 2017-047
Does Skin Cancer Differ by Metropolitan Status by Gender?

Purpose: Skin cancer is a major health concern in the general population, but there are conflicting findings regarding its relationship to where people live. The purpose of this study was to determine whether skin cancer differs by metropolitan status in adults aged 18 and older by gender.

Methods: This cross sectional analysis used 2015 BRFFS data for males and females aged 18 years and older from Florida, North Carolina, and Tennessee. Multiple logistic regression analysis was used to assess the relationship between skin cancer and metropolitan status while controlling for cancer diagnosis, general health, educational level, employment status, income level, ethnicity, age, and gender.

Results: Few participants in the target population reported ever being diagnosed with skin cancer (9-16%), and 4-35% reported living in a rural region, while 22-58% reported living in a suburban area and 38-49% living in an urban area. After controlling for health, socioeconomic and demographic factors, skin cancer and metropolitan status were significantly related. Skin cancer also differed by ethnicity and age (moderate to large effect sizes) for both genders.

Conclusions: This study found that skin cancer was significantly related to suburban metropolitan status amongst adults aged 18 and older in the general population. Limitations to this study include a broad definition of skin cancer and no lifestyle variables specific to sun exposure. It is recommended that general practitioners screen, educate, and provide referral services as necessary.

Sponsor: N/A
IRB/IACUC#: 2017-070
Nutrition Intervention in Pediatric Acute Lymphoblastic Leukemia Patients with Down Syndrome

Purpose: Children and adolescents with Down Syndrome (DS) are more likely to become overweight or obese than those without DS. Additionally, children with DS develop acute lymphoblastic leukemia (ALL) at higher rates than the general population, and pediatric ALL treatment is associated with excessive weight gain. Despite DS-ALL patients’ increased risk for obesity and its complications, there remains a lack of research on preventing weight gain in this specific population. Our objective was to determine if a three-visit nutritional intervention in maintenance therapy was effective at reducing weight gain in DS-ALL patients.

Methods: In a retrospective analysis, medical records of the intervention group were compared to historical controls on the same ALL treatment protocol. Anthropometrics were collected throughout intensive therapy and at every monthly visit during the 12 months of maintenance therapy.

Results: Nine patients met the inclusion criteria: 5 males, 7 Caucasian and 2 Hispanic, and 5 on high risk protocols. The median age was 4.07 years (range, 1.60-14.26). Three and five patients had unhealthy BMIs at diagnosis and month 12 of maintenance, respectively. When comparing patients who had healthy BMIs at diagnosis, the intervention group had smaller increases in BMI than the control group. However, patients who had unhealthy BMIs at diagnosis had unhealthy BMIs at month 12 of maintenance therapy, regardless of intervention.

Conclusions: These results provide evidence that DS patients do tend to gain weight during treatment for ALL, but the data were insufficient to determine whether the nutrition intervention was successful for this population. To our knowledge, this is the first study to investigate obesity prevention in DS-ALL patients. One approach for future studies is an inter-institutional collaboration to obtain a sample size large enough to draw conclusions using inferential statistics.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Recurrence of Sub-Acute Methotrexate Neurotoxicity in a 16-year-old Female Undergoing Therapy for Precursor B-cell ALL

Introduction: Methotrexate, an anti-folate, is commonly used in treatment for acute lymphoblastic leukemia. Neurotoxicity is a known complication of methotrexate and can present as acute, sub-acute, and long-term neurotoxicities.

Sub-acute methotrexate neurotoxicity can be seen as late as two weeks after methotrexate administration and can present as stroke-like symptoms, seizures, aphasia, and encephalopathy. Patients who develop methotrexate neurotoxicity can be safely re-challenged with the drug, although there are reports of recurrent neurotoxicity occurring.

Patients who develop methotrexate neurotoxicity often have MRI findings of white matter hyper-intensities known as leukoencephalopathy. These changes are usually transient and can be present in an asymptomatic patient being treated with methotrexate.

Case Presentation: This case was identified and reviewed using electronic medical records and imaging. Details of the case were also supplied by the patient herself during interview. A 16-year-old female presented to her outside pediatrician with several months of headaches, one week history of loose stools, and two-day history of bruising to the back of the hands. A complete blood count revealed anemia, thrombocytopenia, and leukocytosis. The patient was sent to Cook Children’s Emergency Room.

A diagnosis of precursor B-cell Acute Lymphoblastic Leukemia, High Risk was established. Patient was enrolled in the COG protocol AALLO8B1 for biology and tissue banking and treatment protocol AALL1131. Induction began as planned. The patient was given intrathecal methotrexate on day 8 and 29 without problems. However, her minimal residual disease at the end of induction was 0.2%. Due to this, the patient was switched to the very high-risk arm of protocol AALL1131. The Consolidation phase consisted of weekly intrathecal methotrexate, intravenous cyclophosphamide, intravenous cytarabine, and 6-mercaptopurine. During the first few days of consolidation the patient began complaining of trouble with concentration and memory.

Approximately eleven days after intrathecal methotrexate administration, the patient reported to the Cook Children’s Emergency Department with complaints of pain in her mouth, difficulty swallowing, and a fever of 101.9 degrees Fahrenheit. The patient also had weakness in her right upper extremity, slurred speech, and she could not write with her right hand. Physical exam in the emergency department was remarkable for right facial hemiparesis and asymmetry. She was somnolent and lethargic. The right upper extremity had decreased tone and strength compared to the left upper extremity. The patient exhibited aphasia. Cranial nerve seven demonstrated a right central palsy, but all other cranial nerves were intact. Blood cultures were negative. The patient had to be intubated and transferred to the PICU due to loss of gag reflex and inability to keep her airway open. MRI showed bilateral periventricular white matter and centrum semiovale diffusion restriction with no mass effect consistent with acute methotrexate toxicity. Decadron and Leucovorin were started. She was extubated on PICU day 4.
The patient returned to the oncology clinic a few days after discharge and was doing well overall. During this clinic visit, she received a re-challenge of 15 mg of intrathecal methotrexate. Approximately one week after this methotrexate administration, the patient returned to the emergency department with recurrent methotrexate encephalopathy. She complained of a left lower facial palsy, left arm weakness, and difficulty with speech. She was afebrile and physical exam did not show any major neurological abnormalities.

An MRI of the brain showed diffusion restriction in bilateral centrum semiovale and supratentorial periventricular white matter with right more than left side. This was deemed to be consistent with methotrexate neurotoxicity. MRA showed no vascular deficit.

The patient was switched from intrathecal methotrexate to intrathecal cytarabine for maintenance therapy. She tolerated this well, although she did have some delayed clearance of the methotrexate requiring a longer hospital stay.

Conclusion: Although re-challenge is considered safe, it is important to be aware of the possibility of a second episode of methotrexate neurotoxicity occurring as seen in this patient. The patient had stroke-like symptoms that resolved in a few days in both instances. Additionally, her MRI findings are consistent with leukoencephalopathy. She continues to receive intravenous methotrexate but is given intrathecal cytarabine rather than intrathecal methotrexate.

Sponsor: N/A
IRB/IACUC#: N/A
**Novel therapeutic formulation for the anticancer drug valrubicin using human serum albumin and D-alpha-tocopheryl polyethylene glycol 1000 succinate**

**Purpose:** Human serum albumin (HSA) and the bioavailability enhancer D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) are recognized as versatile biocompatible ingredients in drug nanoformulation. Due to its lipophilicity, the anticancer drug valrubicin is currently solubilized in cremophor EL which does not favor systemic delivery. Hence, even though valrubicin is less toxic and more potent than its widely used anthracycline parent compound doxorubicin, its administration and use are respectively restricted to intravesical route and bladder cancer. Since HSA is able to transport endogenous lipophilic compounds in the blood, and TPGS forms micelles, HSA and/or TPGS could increase the solubility of valrubicin in a preparation and extend its administration to alternative administration routes including systemic delivery. Thus, the goal of this study is to characterize and compare three formulations: HSA-Valrubincin (Val), TPGS-Val and HSA-TPGS-Val.

**Methods:** The formulations were prepared using 0.5mg/mL Val, 50mg/mL HSA and different concentrations of TPGS. Each formulation was continuously stirred at room temperature for 2 hours. Centrifugation and filtration were used to remove unbound valrubicin. The particle size was estimated by dynamic light scattering while the amount of valrubicin incorporated was derived from absorbance reading at 490 nm.

**Results:** Whereas only 61.5% of the feeding valrubicin was incorporated in the HSA-Val formulation, the amount of Val dissolved in TPGS followed the ratio of 1:6 (mol/mol). Addition of increasing amount of TPGS to HSA increased the amount of Val incorporated in HSA-TPGS-Val formulations. The mixture of 50mg/mL HSA, 0.5 mg/mL TPGS and 0.5 mg/mL Val showed 76% of Val incorporation and also displayed the lowest particle size with the highest homogeneity (56 nm±15.3, polydispersity index (PDI) 0.148).

**Conclusion:** Although TPGS concentration could be a limiting factor for drug loading efficiency in TPGS-Val preparations, the combination of TPGS and HSA show the promise of an acceptable formulation. Perhaps, the optimization of HSA-TPGS-Val preparations can be achieved by reducing disulfide bridges in HSA to uncover more hydrophobic sites on the molecule.

**Sponsor:** SBIR 1 R43 CA203170-01

**IRB/IACUC#:** N/A
Hypothesis:
Cardiac toxicity is one of the leading contraindications to many chemotherapeutic agents including anthracyclines (e.g. Doxorubicin). It has been demonstrated that knocking out the beta isozyme of topoisomerase II in mice results in amelioration of the cardiotoxic effects of Doxorubicin. The purpose of this study is to evaluate whether or not the inhibition of the Topoisomerase II beta isozyme by the drug BNS-22 in cardiomyocytes can alleviate the cardiotoxic effects of doxorubicin.

Methods/Materials:
Cardiomyocyte cells (H9C2) were used to evaluate the cytotoxicity of BNS-22. Additionally, these cardiomyocytes were used to determine the rate of cardiac cell death in cells treated with Doxorubicin and BNS-22 concurrently compared to cells treated with Doxorubicin alone. Cell viability was measured by luminescence assay using the CellTiter-Glo kit. Cell viability was measured 72 hours after the administration of Vehicle (control) or BNS-22 or doxorubicin or doxorubicin and BNS-22.

Results:
Cardiomyocytes (H9C2) were grown following standard cell culture conditions. Cells which were treated with both Doxorubicin and BNS-22 together and the cells treated with only BNS-22 suffered considerably less cell loss than the cells treated with Doxorubicin alone.

Conclusions:
These preliminary results suggest that BNS-22 helps to alleviate the cardiotoxic effects of Doxorubicin. This experiment provides some evidence for the use of Topoisomerase inhibitors in the treatment of doxorubicin induced cardiotoxicity. Further cell viability assays using this drug will be performed to substantiate current findings.

Sponsor: Dane Eskildsen supported by the TCOM Honors Research Practicum
IRB/IACUC#: N/A
Slow-growing benign tumors with potential for functional disability in Neuroblastoma: a case study.

Background: Neuroblastoma (NBL) is the most common malignant extracranial tumor in pediatrics and may mature into ganglioneuroma (GN). Though GN is benign, it has the potential to cause severe symptoms related to adjacent structures or organs. Cases of GN causing complications such as scoliosis and hydrenephrosis have been reported. We report a rare case of stage IV neuroblastoma which, over the course of 19 years, has presented as numerous GN tumors causing a striking number of complications.

Case information: A 7 month-old male presented with stage IV NBL disseminated to his face, groin area, and testicles. The primary tumor was resected after chemotherapy treatment. Despite treatment efforts, disease spread to the bone marrow and numerous tumors appeared throughout the body. At the current age of 19, the patient has endured a lifetime of complications due to tumors in the face, spine, intestine, groin, and testicles. These complications include scoliosis, bowel obstruction, severe abdominal pain, hydrenephrosis, varicocele, and neurologic symptoms.

Conclusions: In more than half of patients, NBL is widely metastatic by the time it is diagnosed. Recurrence of NBL or GN is infrequent with complete tumor excision. However, due to the invasive character of NBL, it is difficult to ensure complete elimination of tumor cells. It is possible that the recurrent GN tumors appearing in this patient are the result of the maturation of what was initially metastasized, microscopic NBL lesions. Due to the rarity of such extensive GN dissemination, the pathology and management strategy of this condition is still being understood. Treatment of patients with NBL requires long-term, multidisciplinary management by experienced providers. Emphasis should be placed on quality of life. In addition, transfer of these patients from pediatric care to adult care requires extensive communication and education between the patient, family members, and all involved medical providers.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Scale up of nanolipomer microfluidic production for potential clinical trials

Purpose: The process of optimization and fabrication of nanoparticle synthesis for preclinical studies can be challenging and time consuming. Traditional small scale laboratory synthesis techniques suffer from batch to batch variability. Additionally, the parameters used in the original formulation must be re-optimized due to differences in fabrication techniques for clinical production. Several low flow microfluidic synthesis processes have been reported in recent years for developing nanoparticles that are a hybrid between polymeric nanoparticles and liposomes. However, use of high flow microfluidic synthetic techniques has not been described for this type of nanoparticle system, which we will term as nanolipomer. We hypothesize that it is possible to manufacture nanolipomers in large batches using a high flow microfluidic synthesis method and these nanolipomers will maintain optimal physicochemical and functional parameters.

Methods: Nanolipomers were synthesized through a microfluidic process utilizing the Nanoassembler platform. Nanolipomer size and zeta potential were measured through dynamic light scattering techniques. Time resolved lifetime and anisotropy experiments were performed to verify drug loading. MTT assay was performed on C4-2B prostate cancer cells to assess cell viability after treatment with nanolipomers. Nude mice were intravenously injected with nanolipomers to determine in vivo biocompatibility.

Results: The optimal total flow rate for synthesis of these nanolipomers was found to be 12 ml/min and flow rate ratio 1:1 (organic phase: aqueous phase). The PLGA polymer concentration of 10 mg/ml and a DSPE-PEG lipid concentration of 10% w/v provided optimal size, PDI and stability. Drug loading and encapsulation of a representative hydrophobic small molecule drug, curcumin, was optimized and found that high encapsulation efficiency of 58.8% and drug loading of 4.4% was achieved at 7.5% w/w initial concentration of curcumin/PLGA polymer. The final size and polydispersity index of the optimized nanolipomer was 102.11 nm and 0.126, respectively. Functional assessment of uptake of the nanolipomers in C4-2B prostate cancer cells showed uptake at 1 hour and increased uptake at 24 hours. The nanolipomer was more effective in the cell viability assay compared to free drug. Finally, assessment of in vivo retention in mice of these nanolipomers revealed retention for up to 2 hours and were completely cleared at 24 hours.

Conclusions: In this study, we have demonstrated that a nanolipomer formulation can be successfully synthesized and easily scaled up through a high flow microfluidic system with optimal characteristics. The process of developing nanolipomers using this methodology is significant as the same optimized parameters used for small batches could be translated into manufacturing large scale batches for clinical trials through parallel flow systems.

Sponsor: CPRIT
IRB/IACUC#: 2014/15-18-A04
Current landscape of immunotherapy clinical trials in prostate cancer

Purpose

The number of immunotherapies that have been approved in recent years has generated a lot of enthusiasm in the field of oncology. This success has come on the results of approvals for immunotherapy drugs and the expansion of indications for a variety of hematological and solid malignancies. However, very few immunotherapies have demonstrated improved overall survival in treating patients with prostate cancer. This is due to several factors including tumor heterogeneity, limited prostate tumor-associated antigens, and an immunosuppressive environment. Despite these challenges, numerous clinical trial efforts are ongoing to determine outcomes of immunotherapies in prostate cancer, and many are in the context of combination strategies. The purpose of this project was to identify and categorize the current landscape of immunotherapies that are in clinical trials for prostate cancer.

Methods

An extensive evaluation of the all currently registered clinical trials in the United States of immunotherapies in the setting of prostate cancer was performed utilizing www.clinicaltrials.gov on 1-20-18. The following search parameters were used: Condition/disease: “prostate cancer” Other terms: “immunotherapy”, “CAR-T cell therapy”, “monoclonal antibody”, “checkpoint inhibitors”, and “vaccine”.

Results

The query resulted in a total of 215 registered clinical trials. Most of these trials (84%) were in the context of vaccine therapy against prostate cancer, 12% of trials involved checkpoint inhibitors, and 4% were testing CAR-T cell therapy. Only 6% of the trials were in the phase 3 setting while 32% and 60% were in phase I or phase II, respectively (the remainder were not categorized into a phase). The majority of these trials used combination strategies.

Conclusion

The slow-growing nature of prostate cancer in many patients makes this cancer uniquely suitable for utilizing immunotherapies that may need time to allow for an immune response to mount against cancer cells. There is a tremendous amount of clinical trials that are currently being performed on prostate cancer with a variety of immunotherapeutic strategies. Although more research needs to be done, the potential of a durable and sustained response with immunotherapies is encouraging in the setting of prostate cancer.
Does the Relationship Between Skin Cancer and Obesity Differ Between Young Adult Males Versus Elderly Males?

Purpose: Obesity is an established risk factor for several cancer types, but there are conflicting findings about the relationship between obesity and skin cancer especially in males. Therefore, the purpose of this study was to explore whether the relationship between obesity and skin cancer differs between young adult males and elderly males.

Methods: This cross-sectional analysis used 2015 BRFSS data for males ages 18-40 and ages 65 and older from Alabama, Kentucky, Tennessee, and West Virginia. Multiple logistic regression analysis was used to assess the relationship between skin cancer and obesity while controlling for age, White ethnicity/race, educational level, tobacco use, alcohol use, healthy eating, and routine checkups.

Results: Few participants reported ever being diagnosed with skin cancer (13-17%) and about one-third reported being obese (28-33%). Results of adjusted analysis indicated that skin cancer and obesity were not significantly related in any state, but skin cancer differed by age and ethnicity/race (large effect sizes) in all four states.

Conclusions: Overall, obesity was not related to skin cancer in any of the four states in young and elderly males, but skin cancer differed by age and ethnicity/race in all four states. Although this study was restricted to a single time-point survey, the broad range of the BRFSS survey allows the results to generalize to the general population in the primary care setting. Due to the low to moderate prevalence of obesity, primary care providers should educate patients on its harmful effects while the low prevalence of skin cancer indicates providers should only screen patients with symptoms. Since there is no association between obesity and skin cancer, these conditions should be considered separately.

Sponsor: N/A
IRB/IACUC#: 2017-070
Evaluation of Stability and Anti-cancer activity of Copper(II) Tolfenamic Acid with an emphasis on Pancreatic

Purpose: Tolfenamic acid (TA) acts as an anti-cancer agent in several cancer models via down-regulating transcription factors Sp1 and Sp3, and an inhibitor of apoptotic protein, survivin. Copper (Cu) is an important element with multiple biological functions and has gained interest in medical applications. Recently, Cu-TA has been synthesized and tested for enhanced therapeutic activity. In this study, Cu-TA was investigated for its stability and anti-cancer activity using several cancer cell lines and mouse model for pancreatic cancer (PC).

Method: Cu-TA was synthesized and characterized by UV visible spectroscopy and Fourier-transform infrared spectroscopy (FTIR). Anti-proliferative activity was evaluated against twelve cell lines representing six (breast, colon, glioblastoma, medulloblastoma, pancreatic and prostate) cancers using the CellTiter-Glo kit and compared with TA. Further studies were performed using PC cells. The expression of Sp1, Sp3 and survivin was determined by Western blot and qPCR. The stability of Cu-TA was determined using 8-12 month-old powder and six-month-old stock solution. Cardiomyocytes (H9C2) were used to test the cytotoxicity in non-malignant cells. Athymic mice were injected with PC cells and treated with vehicle (control) or 25 or 50 mg/kg of Cu-TA 3 times/week and the effect on tumor growth was monitored for 4 weeks Animals body weight changes were also observed to determine overt toxicity.

Results: Cu-TA significantly more effective than TA against all tested cancer cells. The IC50 values of Cu-TA were 30 to 80% less when compared with TA. Comparison of the twelve-month-old powder and six-month-old stock solution using the Panc1 cells showed similar IC50 values.

Conclusion: These in vitro and in vivo studies demonstrate that Cu-TA is more effective than TA and potentially useful as an effective anti-cancer agent.

Sponsor: N/A
IRB/IACUC#: 2017-0040
Diffuse Large B cell Lymphoma presenting as Acute Pancreatitis

Background:

Diffuse large B cell Lymphoma (DLBCL), not otherwise specified (NOS) is the most common type of lymphoma in the world accounting for 25–30% of Non-Hodgkin lymphomas (NHL). It is more common in the elderly but occurs in all age groups and predominantly affect the male. Most common sites of involvement include lymph nodes or extranodal sites (bone, skin, thyroid, gastrointestinal tract and lung). Only 1.25% to 2.2% of all patients with NHL have pancreatic involvement at presentation. Primary pancreatic lymphoma (PPL) rarely presents with the typical B symptoms observed in lymphoma (ie, weight loss, fever, or night sweats). Here we report an unusual and rare case of PPL which was first diagnosed as acute biliary pancreatitis that was later found to be Pancreatic Adenocarcinoma and later confirmed on biopsy as DLBCL-NOS.

Case Report:

An 80-years-old caucasian male presented to the ER with complaints of abdominal pain for one day, generalized weakness and shortness of breath for two weeks. ROS otherwise unremarkable. Vitals showed elevated blood pressure otherwise unremarkable. Physical exam was positive for epigastric tenderness radiating to the back without any signs of peritonitis and labs showed TBili-5.4, DBili-3.6, AST-440, ALT-502, AlkPhos-372, LDH-388, Amylase-268, Lipase-4403. Beta-2-microglobulin-2.4, AFP-1.5, CEA-0.7, CA 19-9-178. Patient had a prior history of Prostate CA status-post radiation. CT Abdomen showing a pancreatic mass with biliary and duodenal obstruction suggestive of a tumor. CT Abdomen and pelvis with contrast was suggestive of Pancreatic Adenocarcinoma. Patient was diagnosed with acute biliary pancreatitis and was started IVF and pain medication. He subsequently underwent placement with a biliary drain to relieve obstruction. Biopsy was suggestive of DLBCL-NOS. Patient was started on CHOP-R regimen and advised to have a close follow up with oncologist as an outpatient. As treatment progresses, biliary drain will be replaced by indwelling stents to relieve the obstructions.

Discussion:

PPL is a rare neoplasm that can mimic pancreatic adenocarcinoma in many aspects. Arriving to a proper diagnosis using both biochemical and tissue biopsy is very essential as it carries excellent prognosis if diagnosed early. The best therapeutic option as per the study by Behrns et al and many other recent studies is chemotherapy CHOP-R with or without surgical resection and radiotherapy depending on the Ann Arbor staging and is associated with increased long-term survival of PPL.
The Involvement of S6 Kinase-2 in Breast Cancer

Purpose: Breast cancer is the second leading cause of cancer death in women. Triple negative breast cancer is characterized by the lack of estrogen receptor, progesterone receptor, and HER2/neu and hence poses a problem for targeted therapy. Thus there is an urgent need to identify a suitable molecular target. The 40S ribosomal protein S6 kinase (S6K) acts downstream of mTOR, which plays important roles in cell proliferation, protein translation, and cell survival and is a potential target for cancer therapy. S6K exists as two homologues, S6K-1 and S6K-2, but little is known about the function of S6K-2. Although Akt is believed to act upstream of mTOR, persistent inhibition of S6K-1 can activate Akt via a negative feedback loop. In the present study, we have examined the effects of S6K-2 on Bcl-2. Bcl-2 is in the Bcl-2 family of proteins and is an anti-apoptotic protein.

Methods: The breast cancer cell lines ZR-75 and MCF-7 were used. These cells were transfected using siRNAs which were either control non-targeting or target-specific. The extent of gene knockdown was determined by Western blot analysis. The proteins from the cell extract were visualized using SDS-PAGE gel electrophoresis and enhanced chemiluminescence. Yo-Pro staining was used to visualize apoptotic cells.

Results: It was noted that S6K-2 knockdown lead to a decrease in Bcl-2, this occurred concurrently with an increase in cell death. Silencing of S6K-2 caused a decrease in Bcl-2 via Akt.

Conclusion: Targeting S6K-2 may be an effective therapeutic strategy to treat breast cancer.

Sponsor: N/A
IRB/IACUC#: N/A
Bone Sectioning Technique for 3D Confocal Image Resolution and Capture of Dye-Loaded Nanotherapeutics

Purpose: Capturing detailed images of bone architecture has unique challenges and conventional procedures have proved to be insufficient for molecular 3D imaging. Furthermore, traditional 2D immunohistochemistry provides limited information for assessing therapeutic localization in the bone. In addition, techniques such as thin paraffin sections visualized by immunofluorescence microscopy or transmission electron microscopy, require prolonged exposure to damaging decalcification reagents. These chemicals have destructive effects on bone morphology and limit the capture of proteins. The objective of this project was to develop an adapted protocol for bone tissue preparation prior to sectioning and immunohistochemical (IHC) staining. This method enables ultra-thick sections for enhanced Z-stacking, enables the generation of high-resolution 3D images that map the bone tissue, and provides oseo-spatial detection of our dye-loaded nanotherapeutics.

Methods: Bones were decalcified then incubated in cryoprotectant before emersion in the embedding solution. Samples were frozen at -80. Ultra-thick sections were made on a Thermo Fisher Cryostar NX70 Cryostat (75 – 100 m) and placed on polar slides. Immunohistochemical staining was applied to the slides, which were imaged with a Zeiss LSM 510 confocal microscope. Our therapeutic was labeled with near fluorescent dye. Results: High-fidelity, 3D images of mouse tibia and femur were imaged. Furthermore, visualization of nuclear staining, bone epithelial cells, and the fluorescently labeled therapeutics were easily detected. Thick sectioning provided us with a more robust, tomographic image, allowing for more thorough mapping and analysis of the nanotherapeutics in the bone.

Conclusions: Our modified protocol for processing and imaging bone is an effective approach to bone handling, confocal imaging, and detecting bone and dye-labeled nanotherapeutics. This approach will provide benefits for facilitating our understanding of the significance that drug localization has on the bone microenvironment and its impact on therapeutic efficacy.

Sponsor: N/A
Documentation of Substance Use in Adolescent and Young Adult Cancer Patients

Background: Cancer remains the leading cause of disease-related death in the Adolescent and Young Adult (AYA) population, ages 15-39. One psychosocial circumstance influencing the management of this population is substance use. Substance use can impair judgement which may affect patient adherence to treatment protocol. Substance use may lead to poorer health outcomes and can increase the risk for secondary malignancies. It is important for clinicians to ask about substance use in AYA patients so they can prevent these adverse effects.

Purpose: The purpose of this study was to examine the quality of the documentation of substance use behaviors among this population at Cook Children’s Medical Center (CCMC) before and after the implementation of an AYA program at CCMC in 2011.

Methods: This study used a retrospective analysis of patient charts aged 15-35 years old at the time of diagnosis who were treated at CCMC between 2008 and 2014. Patients with brain and thyroid tumors were excluded. Quality of documentation was compared before and after the AYA program was started. The variables collected include documentation of tobacco, alcohol, and illicit drug use before and during treatment. Chi-square analyses and odds ratios (OR) were used to compare rates of documentation.

Results: There were 169 patients who met inclusion criteria. Clinician documentation of history of substance use was highest with tobacco use (72%) followed by alcohol use (32%) and drug use (30%). Additionally, documentation was significantly better after the implementation of the AYA program for tobacco use before (p<.0001; OR=1.75), treatment.

Conclusions: Providers were more likely to document tobacco use than alcohol or drug use. Documentation improved after a programmatic focus on AYA care was established. Despite this, most charts reviewed did not document alcohol or drug use, so thorough and consistent documentation is still needed in order to see if there is a relationship between these variables and the outcomes of AYA patients.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Blocking LLT1-CD161 interaction enhances natural killer cell-mediated lysis of triple-negative breast cancer cells

Purpose: Triple-negative breast cancer (TNBC) accounts for 20 percent of all breast cancer cases and is known to be the most invasive form of breast cancer. TNBC’s absence of estrogen, progesterone, and human epidermal growth factor-2 receptors makes utilizing hormonal treatments ineffective in suppressing tumor growth. TNBC is associated with poorer prognosis and higher incidences of relapse. Therefore, natural killer cell-mediated immunotherapy shows potential as a treatment option for TNBC. Natural killer cells (NK) are innate lymphoid cells that serves its role in the immune system to eradicate infected and tumor cells. NK cell function is regulated through its receptors interacting with activating and inhibitory ligands on target cells. Lectin-like Transcript-1 (LLT1, CLEC2D) is a counter-receptor that interacts with CD161 (NKRP1A) and inhibits NK cell activation. Our study demonstrated that by blocking TNBC’s LLT1 interaction with CD161 with antibodies increases lysis of TNBCs by NK cells.

Methods: We have identified the expression and function of LLT1 on TNBC cell lines MDA-MB-231 and MDA-MB-436 by flow cytometry, western blot, immunofluorescent microscopy, and chromium-release assay. LLT1 expression at the cell surface was decreased through gene knockdown with small interference RNA (siRNA) transfection. Primary NK cells were isolated from peripheral blood mononuclear cells from healthy individuals and then were co-incubated with chromium-labeled TNBCs for quantification of specific lysis of TNBCs by NK cells.

Results: Our results have demonstrated a higher expression of LLT1 on TNBCs than non-tumorigenic breast cell line MCF10A. We have shown that blocking LLT1 interaction with CD161 with antibodies on TNBCs have increased lysis of TNBCs by primary NK cells. We have also shown that gene knockdown of LLT1 decreases cell surface expression of LLT1 on TNBCs and increases lysis of TNBCs by NK cells.

Conclusions: LLT1 expressed on TNBCs is a ligand that interacts with NK receptor CD161 and sends an inhibitory signal to the NK cell thus serving its role for TNBCs to evade immunosurveillance. Respectively, blocking LLT1 with antibodies on TNBCs and decreasing expression of LLT1 by gene knockdown increases susceptibility of TNBCs to NK cell-mediated lysis. Blocking interaction between LLT1 and CD161 with antibodies activates lysis by NK cells and will open a possible new immunotherapeutic strategy for patients diagnosed with TNBC.

Sponsor: UNTHSC Seed Grant & NIH Grant NS101481 to PM

IRB/IACUC#: 2008-094
Evaluation of Metformin as an anti-cancer agent in Medulloblastoma

Purpose: Medulloblastoma (MB) is the most common malignant brain tumor in children under 16 years of age. Standard treatment, including surgery, chemotherapy, and radiation, is successful for most; however, survivors often suffer from long-term neurocognitive and growth potential related sequelae. Therefore, there is a need to understand the molecular processes regulating MB growth to find less toxic therapies. Survivin is a protein in the Inhibitor of Apoptosis Protein (IAP) family that inhibits caspase activity. Survivin is highly expressed in MB and associated with a poor prognosis. Specificity protein 1 (Sp1) is a transcription factor regulating survivin expression and is overexpressed in many cancers. Interestingly, the use of Metformin (MET), an anti-diabetic drug, correlated with decreased occurrence of several cancers. Previous studies have demonstrated its anti-cancer activity in breast cancer cells as well. The objective of this study is to test the effect of MET on MB cells in vitro.

Hypothesis: We hypothesize that MET treatment decreases the growth of MB cells in a dose and time-dependent manner, possibly inhibiting the expression of survivin via downregulating Sp1.

Methods: DAOY (MB cell line from American Type Culture Collection) cells were treated with increasing concentrations of MET (0, 1, 5, 10, and 20 mM). Cell viability was assessed at 24 and 48 hours post-treatment using the CellTiter-Glo cell viability assay. Survivin and Sp1 expression in MET treated cells was determined by Western blot analysis. Potential mechanism of cell proliferation inhibition was investigated by measuring the induction of reactive oxygen species (ROS) through Flowcytometry.

Results: MET treatment resulted in decreased cell viability in a dose and time dependent manner. MET treatment also decreased Sp1 and survivin expression indicating that the effect of MET is mediated via Sp1 transcription factor. We also observed MET induced cellular ROS formation, which could be a potential anti-cancer mechanism.

Conclusion: Our data demonstrates that MET can inhibit MB cell growth, possibly via targeting Sp1 to down-regulate survivin and inducing ROS. We conclude that MET has the potential to be used in the treatment of MB. Due to limitations of using Metformin alone as an anti-cancer agent, additional experiments are underway to determine its use in conjunction with MB specific chemotherapeutic agents.

Sponsor: N/A
IRB/IACUC#: N/A
Two Tumors in One: Mixed Malignant Germ Cell Tumor with Rhabdomyosarcomatous Malignant Transformation in a Pediatric Patient

Background

Testicular germ cell tumors (GCT) are the most common malignancy in males aged 15-34. The transformation of GCTs into secondary somatic-type malignancies is rare, and the lack of clear treatment guidelines presents a clinical challenge for treating physicians especially when chemosensitivities do not overlap. This report will focus on one case of a mixed malignant GCT with a secondary somatic-type malignancy. We highlight our experience in diagnosing and treating this tumor, and through literature review suggest treatment guidelines for treating a pediatric patient with similar tumor presentation.

Case Information

We report a 15-year-old male previously in good health who complained of a painless hard mass involving his right testicle following surgical repair of bilateral varicocele. A right radical orchiectomy was performed, and surgical resection was achieved with negative margins. Histopathological examination of the mass showed a mixed non-seminomatous malignant GCT with an embryonal rhabdomyosarcoma component that made up more than half of the primary tumor. Our greatest challenge in treating this tumor was understanding how to target the disparate components. The two major components of the tumor were staged and treated separately. The GCT component was deemed low risk, and following surgery, active surveillance strategies were utilized. The rhabdomyosarcoma component, also characterized as low risk, was targeted with chemotherapy in a 24 week therapy schedule with 4 cycles of vincristine, dactinomycin, and cyclophosphamide followed by 4 cycles of vincristine and dactinomycin. The patient completed therapy without complications. 34 months post therapy he remains in good health and has shown no evidence of tumor recurrence.

Conclusion

Cases such as these remain challenging given the lack of consensus in treating two malignancies whose chemosensitivities do not overlap. There is little debate that successful surgical resection aimed towards securing negative margin remains key in adequate treatment of those with localized disease. With regard to choice of chemotherapy postoperatively, there is some suggestion that malignant transformation of GCT responds poorly to cisplatin based therapy. In treating a pediatric patient with similar tumor presentation, we suggest that choice of chemotherapy agents should be influenced by the transformed histological element as the transformed element may not be responsive to cisplatin-based therapy.

Sponsor: N/A

IRB/IACUC#: CCHCS-IRB
Anti-cancer activity of biogenic silver nanoparticles against Neuroblastoma cells

Purpose: Neuroblastoma (NB) is one of the solid tumors diagnosed in young children. Due to severe side effects associated with the current therapeutic options, it is important to identify less toxic therapies for treating NB patients. Nanoparticles (NPs) are widely used in various medical applications; however, the particle size and preparation methods play critical roles in their activity. Recently use of plant extracts as stabilizing or reducing agents is gaining significance due to higher stability and activity. Biogenic silver nanoparticles (BSNPs) have been tested for their activity in wound healing mechanism and preventing microbial diseases. The objective of this investigation was to prepare BSNPs using plant extracts and silver nanoparticles and evaluate their anti-cancer activity against neuroblastoma (NB) cell lines. BSNPs were prepared using two different plant extracts and characterized. SHSY5Y and LA155n cells were treated with increasing concentrations of BSNPs for 48 h and dose curves obtained. The effect of BSNPs on apoptosis and cell cycle arrest was evaluated to understand the underlying mechanisms.

Method: BSNPs were synthesized using silver NPs and herbal reducing agents. These particles were characterized by Atomic Force Microscope and Transmission Electron Microscope. Fourier-transform infrared spectroscopy was used to identify the active herbal compounds along with silver nanoparticles. The cell viability of NB cells was measured using Cell Titer-Glo kit. Apoptotic cells distribution were determined by Flow cytometry using annexin V staining. The expression of cleaved Poly (ADP-ribose) Polymerase (cPARP) was evaluated by western blot.

Results: The characterization of BSNPs revealed alkynes, amines and alkylhalides as reducing agents and particles were ranged 20-100 nm in size. BSNPs caused significantly more cell growth inhibition when compared to silver NPs which is accompanied by an increase in apoptotic markers, c-PARP expression and annexin-v staining.

Conclusion: These preliminary data using different reducing agents suggest the potential anti-proliferative effect of BSNPs against NB cells.

Sponsor: Indian Council of Medical Research, INDIA
IRB/IACUC#: N/A
Challenges of Medical Decision-Making in an Autistic Pediatric Patient with Retinoblastoma and Osteosarcoma: A Case Study

Background: In oncology, one of the most crucial decisions is whether it is appropriate to discontinue chemotherapy before the full course of treatment. Medical professionals must consider the risks versus the benefits, the patient’s quality of life, the appropriate role of chemotherapy, and the patient’s preference. The decision is difficult in pediatric patients who have encountered multiple malignancies while suffering from the untoward effects of chemotherapy. It is especially difficult in malignancies such as osteosarcoma where successful treatment involves the full course of systemic chemotherapy.

Case Information: A 9-year-old autistic male with a history of retinoblastoma presented with pain in the right leg and an abnormal gait. A biopsy confirmed the diagnosis of high grade osteosarcoma. Neoadjuvant chemotherapy (protocol AOST 0331) was initiated with the administration of Cisplatin and Adriamycin, but was complicated by nausea, vomiting, febrile pancytopenia, and multiple life threatening infections. Nausea and vomiting was so severe that a feeding tube was placed for feedings and medication administration. After hip disarticulation amputation, chemotherapy was resumed, but was suspended at week 15 of treatment due to multiple life-threatening complications such as nephrotoxicity, endocarditis, and staphylococcus and streptococcus mitis infections.

Discussion: The decision to discontinue chemotherapy early was not an easy one. The patient suffers from severe autism, is non-verbal, blind, intellectually disabled, and suffered many complications from his first and second pediatric malignancies. After considering the patient’s long battle with two pediatric malignancies and the numerous challenges he has had from undergoing chemotherapy, the patient’s parents and physicians agreed to discontinue chemotherapy. The patient is now receiving palliative care.

Conclusion: Our case illustrates the importance of an individualized treatment plan when working with complicated patients. When physicians are faced with challenging medical decisions, it is important to remember, that with the help of their medical team and open communication with patients and their family members, making these decisions may not be as difficult and may be beneficial to everyone involved.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
MIEN1 Regulates Breast Cancer Cell Migration and Invasion by Altering Cytoskeletal Dynamics Through Focal Adhesion Kinase and N-WASP Signaling

Purpose:
Triple negative breast cancer (TNBC), accounts for approximately 15-20% of all breast cancer diagnoses. This is the most aggressive breast cancer subtype and is characterized by a lack of known receptors associated with, making prognosis and treatment difficult in patients with TNBC. TNBC has a propensity to metastasize to vital organs, including lung, brain and bone. This can occur early in the disease progression and usually leads to the elevated mortality rate in TNBC patients. Research efforts to identify molecular markers within TNBC for prognosis and therapy have not been fruitful. Migration and Invasion Enhancer 1 (MIEN1) has been implicated in the disease progression of many cancers, including TNBC. We determined to further understand the molecular mechanisms by which MIEN1 regulates cell motility and invasion in the context of TNBC. This knowledge will provide a basis to pursue MIEN1 as a potential marker for future treatment and evaluation of TNBC cases.

Methods:
Wild-type MIEN1 (MIEN1-WT) or Immunoreceptor tyrosine-based activation motif (ITAM)-mutant MIEN1 MIEN1-Y39/50F) was overexpressed in MDA-MB-231 cells to evaluate the role of ITAM signaling in MIEN1 mediated migration and invasion. Migration speed and persistence toward a chemoattractant was assessed using microfluidic chambers. Invasion was evaluated by embedding cell aggregates in a 3D collagen matrix and examining the spread of the cells. MIEN1 influence on migration was mediated by actin cytoskeletal dynamics. This mechanism was further delineated by looking at actin polymerization as well as focal adhesion adaptors and signaling molecules using western blotting as well as confocal microscopy. An in vitro kinase assay was also used to evaluate activators of MIEN1.

Results:
MIEN1-WT over-expression in MDA-MB-231 cells resulted increased migratory and invasive capabilities compared to wild-type cells. Additionally, over-expression of the MIEN1-Y39/50F ITAM mutant inhibited the cells’ ability to migrate towards a chemoattractant as well as invade through a collagen matrix. MIEN1 co-localized to the cell membrane with FAK (focal adhesion kinase) and facilitated signaling through N-WASP to alter cytoskeletal dynamics and increase filamentous actin accumulation.

Conclusion:
MIEN1 regulates migration and invasion of TNBC cells by altering cytoskeletal dynamics through activation of FAK and N-WASP, which results in increased actin polymerization and cell motility.

Sponsor: N/A
IRB/IACUC#: N/A
Suppression of glycosidase NGLY1 induces multifaceted anticancer responses.

Purpose: NGLY1 is a pivotal enzyme that catalyzes the deglycosylation of denatured glycoproteins and facilitates proteasome-mediated protein degradation. However, there is limited information regarding the responses of human normal and cancer cells to NGLY1 suppression. The objective of our study is to determine the significance of NGLY1 for melanoma cell viability and how it may be exploited as a novel anticancer target.

Methods: We used cellular and molecular biology tools such as Crispr-Cas9-mediated gene editing and shRNA for NGLY1 suppression. Computational modelling and a rational design approach was used to design and synthesize novel small molecules that can covalently modify NGLY1 to irreversibly inhibit its activity. We also used systems biology approaches including global gene expression profiling and proteomics analysis to uncover mechanisms through which inhibition of NGLY1 preferentially leads to cancer suppression.

Results: Compared with normal cells, NGLY1 was upregulated in melanoma cell lines and patient tumor samples. NGLY1 knockdown caused melanoma cell death in vitro and tumor growth retardation in vivo. Mechanistically, NGLY1 suppression induced pleiotropic responses which can synergize with the anti-melanoma activity of chemotherapy and targeted therapy agents. We have discovered a series of novel small-molecule inhibitors of human NGLY1. Both pharmacological and molecular biology tools that inhibit NGLY1 elicited highly similar responses in melanoma cells. Unlike normal cells, melanoma cells presented distinct responses and high vulnerability to NGLY1 suppression.

Conclusion: Our work represents the first comprehensive characterization of multifaceted anti-melanoma responses by targeting NGLY1. This study revealed the biological significance of NGLY1 in melanoma cells and provided mechanistic insights regarding how NGLY1 inactivation preferentially leads to eradication of melanoma with limited impact on normal cells. Collectively, our findings attest that the inactivation of NGLY1 represents a novel and promising anti-melanoma strategy.

Sponsor: N/A
IRB/IACUC#: N/A
S1Q3T3 Leading to Early Suspicion of Pulmonary Embolism in Low-Risk Patient

Background/Abstract:
Acute pulmonary embolism (PE) may prove fatal without early suspicion and subsequent treatment. Many cases go undiagnosed, with one study showing an estimated 70% of post mortem PE cases were undiagnosed at the time of death.1 Young patients are most at risk of being misdiagnosed as suspicion in this population is very low. Even with a variety of diagnostic modalities a high clinical suspicion remains key for diagnosis.2 The varying degree of clinical presentation makes diagnosing PE very difficult. Here we present a case of a patient with no known risk factors and WELLS score of 0 whose electrocardiogram (EKG) findings led to an early investigation, diagnosis, and subsequent treatment of a massive pulmonary embolism.

Case Report:
A 34 year old AAM with a PMHx of asthma presented to our ED with a chief complaint of substernal chest pain with associated dyspnea. On arrival, the patient was hemodynamically stable with all VS in normal range. CXR showed no acute process. Our team was called to admit the patient from the ED for uptrending troponins and an EKG with inferior lead T-wave inversions. Troponins trended up to 0.255. His EKG showed sinus tachycardia with T-wave inversion in inferior and anterior leads along with S wave in lead I and Q wave in lead III. WELLS score was 0. Though not sensitive, the EKG findings increased our suspicion for PE. D-dimer was ordered and found to be elevated at 6,693. A stat Chest CTA revealed a large saddle pulmonary emboli. LMWH therapy was initiated. Work-up for genetic and acquired factors were negative and patient was discharged on oral anticoagulation.

Discussion/Conclusion:
EKG findings in patients with PE have been a topic of much debate since first reports of investigation in 1935. Over the years medicine has evolved with ubiquitous access to more effective modalities for diagnosing PE. Despite the advent of these other modalities, the diagnosis of PE remains elusive and the prognosis is variable depending on clinical presentation and appropriate diagnosis and treatment.4 While the S1Q3T3 pattern is commonly taught in medical schools around the world as the pathognomonic ECG pattern associated with pulmonary embolism, its reported incidence in acute PE is highly variable with studies showing its incidence anywhere from 10-50%.5 Non-specific ST elevation and T wave inversion in inferior and anterior precordial leads are the most frequently noted EKG abnormalities in patients presenting with acute PE.6 Acute pulmonary embolism in young males without risk factors is rare. Given the time sensitive nature of appropriate diagnosis and treatment of PE, it is
important that health care providers recognize EKG findings characteristic of PE. These findings can incite suspicion in low risk patients and direct subsequent work-up and management in a timely fashion.

Sponsor: N/A
IRB/IACUC#: MCFW-IRB
Responses of cerebral blood flow and tissue oxygenation to low frequency oscillations during simulated hemorrhagic stress in humans

Introduction: Tolerance to both actual and simulated hemorrhage varies between individuals. Low frequency (LF; ~0.1 Hz) oscillations in mean arterial pressure (MAP) and brain blood flow (indexed via middle cerebral artery velocity, MCAv), may play a role in tolerance to reduced central blood volume; subjects with high tolerance to simulated hemorrhage induced via application of lower body negative pressure (LBNP) exhibit greater LF power in MAP and MCAv compared to low tolerant subjects. The mechanism for this association has not been explored. We hypothesized that inducing LF oscillations would attenuate reductions in cerebral blood flow and oxygenation during simulated hemorrhage.

Methods: 11 subjects (9M/2F) were exposed to two LBNP profiles with an average chamber pressure of -60 mmHg: 1) 0 Hz - chamber pressure remained at -60 mmHg for 9-min, or 2) 0.1 Hz - chamber pressure oscillated between -30 mmHg and -90 mmHg at a frequency of 0.1 Hz for 9-min. Profiles were separated by a 5-min recovery. Measurements included arterial pressure and stroke volume via finger photoplethysmography, MCAv via transcranial Doppler ultrasound, and cerebral oxygenation of the frontal lobe (ScO2) via near infrared spectroscopy. Hemodynamic data was analyzed using a paired t-test. Tolerance was assessed with a Fischer’s exact test. Results: No differences were observed between profiles for MAP (0 Hz, 79.8±2.5 mmHg vs. 0.1 Hz, 80.0±1.9 mmHg; P=0.93) and MCAv (0 Hz, 42.4±3.3 cm/s vs. 0.1 Hz, 43.5±3.7 cm/s P=0.43). The reduction in ScO2 was attenuated (P=0.05) during the 0.1 Hz profile (-4.1±1.2 %) compared to the 0 Hz profile (-6.1±1.1 %). A similar attenuation was observed in stroke volume (0 Hz, -42.6±2.5 % vs. 0.1 Hz, -30.6±2.5 %; P Discussion:In partial support of our hypothesis, cerebral oxygenation was protected during the 0.1 Hz OLBNP profile. While MCAv was similar between conditions, the oscillatory pattern of cerebral blood flow may elicit a shear-stress induced vasodilation, so assessment of velocity may mask an increase in flow. Importantly, more subjects were able to tolerate the 0.1 Hz profile compared to the static 0 Hz profile, despite similar arterial pressure responses. These findings emphasize the potential importance of hemodynamic oscillations in maintaining perfusion and oxygenation of cerebral tissue during hemorrhagic stress.

Sponsor: UNTHSC ICMD Junior Faculty Seed Grant
IRB/IACUC#: 2016-049
Acute Effects of Obstructive Sleep Apnea on QT interval

Over 20 million people in the United States suffer from Obstructive Sleep Apnea (OSA). Compared to the general population, OSA patients are 2.6 times more likely to experience sudden cardiac death (SCD), and it is suspected that this is due, in part, to QT prolongation leading to fatal dysrhythmias. We recently showed that 20 min of simulated OSA in healthy young individuals caused significant increases in QTc, however, it is not known what effect actual OSA events have on QT interval and what factors influence these responses. Thus, the purpose of this study was to evaluate whether obstructive apneic events in OSA patients leads to QT prolongation compared to baseline.

Methods: We determined QTc intervals (determined by Bazett’s formula) from the electrocardiograms of 14 patients undergoing polysomnography for diagnosis of OSA and titration of treatment with positive airway pressure. IRB approval was obtained for our protocol (UNTHSC #2018-019). Patients that were selected had an apnea hypopnea index >20/Hr and had no prior myocardial infarction or heart failure. Each patient’s ECG during their sleep study was analyzed to assess QT interval throughout the night. Baseline QT intervals were compared to QT intervals during obstructive apneas before midnight (Early) and apneas after midnight (Late), thus, representing those in which there were few prior apneas (Early) versus those with numerous prior apneas (Late). The QTc intervals were compared between baseline awake and baseline asleep, and between baseline and Late apneas. Statistical comparisons were made with paired t tests.

Results: Baseline QTc intervals were not different between awake and sleep (p > 0.60); however, during apneas (whether Early or Late), the QTc intervals were significantly prolonged (p = 0.008). Conclusions: In conclusion, OSA is often associated with acute QTc prolongation with the magnitude ranging from 5-42 msec in this patient cohort. Further analyses will be performed to determine factors that affect the magnitude of QT prolongation accompanying apneas during the night. In addition, future studies will focus on QTc changes in OSA patients with prior heart disease, as these are the patients at greatest risk for developing serious arrhythmias during the night.

Sponsor: N/A
IRB/IACUC#: 2018-019
Trophoblast cells exposed to hypoxia and oxidative stress release mitochondrial DNA and undergo apoptosis

1. Purpose

Preeclampsia is a syndrome of high blood pressure with end organ damage diagnosed after the 20th week of pregnancy. This syndrome is associated with placental ischemia, oxidative stress, and exaggerated rates of placental cell death. Mitochondrial DNA (mtDNA) that is released in the extracellular space due to mitochondrial damage or cell death has potent pro-inflammatory and pro-immunogenic properties. Circulating mtDNA is increased in plasma from women with preeclampsia compared to healthy pregnant women; however, the cellular origin of mtDNA is unknown. This leads to our hypothesis that trophoblast cells exposed to hypoxic and oxidative stress release mitochondrial DNA and undergo apoptosis.

2. Methods

Human trophoblast cells (BeWo choriocarcinoma cell line) were grown to 80-90% confluency before treatment with: 1) hypoxia (1% O2) vs. normoxia (21% O2) for 6, 15, or 24 h, or 2) an oxidative stress inducer (H2O2, 200 μM for 4 h or 24 h), a mitochondrial complex I inhibitor (Rotenone, 5 μM for 4 h), or untreated control. Absolute real-time PCR quantification of mtDNA was measured on total nucleic acid extracts (Omega Mag-Bind® Blood & Tissue DNA HDQ Kit) from cell culture supernatants using TaqMan® probes and chemistry. Apoptosis was quantified via double staining for Annexin V and propidium iodide using flow cytometry.

3. Results

Concentrations of mtDNA were higher in supernatants from BeWo cells exposed to hypoxia than those exposed to normoxia for 15 h (normoxia: 14.2 pg/μL ± 1.2, n = 3 vs. hypoxia: 20.6 pg/μL ± 0.4, n = 3; p = 0.02). BeWo cells treated with H2O2 showed no increase in mtDNA release after 4 or 24 h (p ≥ 0.34). Cells exposed to hypoxia did not exhibit increased apoptosis after 6, 15, or 24 h (p ≥ 0.25). Incubation with H2O2 for 18 h resulted in increased apoptosis (Untreated control: 15.6%, n = 1 vs. H2O2: 32.5%, n = 1). Treatment with rotenone resulted in increased BeWo cell apoptosis (Untreated control: 18.1% ± 2.6, n = 2 vs. Rotenone: 35.5% ± 2.5, n = 2).

4. Conclusions

Extracellular mtDNA was increased in a trophoblast cell culture exposed to hypoxia, but not when exposed to H2O2. Apoptosis was not increased when cells were exposed to hypoxia but was increased after exposure to inducers of oxidative stress. Future studies will investigate the mechanism by which hypoxia results in release of mtDNA, with focus on determining whether mtDNA release is independent of apoptosis.
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IRB/IACUC#: N/A
Does General Health Differ by Physical Activity Levels in Females Ages 55 and Older with Cardiovascular Disease?

Purpose: For older adults with existing cardiovascular disease (CVD), few studies have examined the benefits of varying levels of physical activity with respect to general health. The purpose of this study was to assess the relationship between general health and physical activity levels in women ages 55 and older with a history of CVD.

Methods: This cross-sectional analysis used 2015 BRFSS data for females ages 55 and older with a history of CVD in Alabama, Arkansas, Louisiana, Mississippi, and Oklahoma. This study analyzed data for three separate conditions related to CVD: stroke, heart attack, and coronary heart disease. Adjusted analysis was conducted to determine the relationship between general health and physical activity levels for each condition while controlling for high blood pressure, diabetes, high cholesterol, weight status, alcohol use, tobacco use, and age.

Results: Across states, there was a low prevalence of CVD in females ages 55 and older (8-10%). Participants with CVD had a moderate prevalence of good general health (32-61%) and low prevalence of highly active physical activity (16-25%). Results of adjusted analysis for each of the three CVD related conditions determined good general health was significantly related to being highly active (moderate-to-large effect sizes) in four out of five states. Additionally, for participants with a history of coronary heart disease, good general health was significantly related to being active (large effect sizes) in four out of five states.

Conclusions: Overall, good general health was found to be significantly related to active and highly active physical activity levels in population based samples for females ages 55 and older with CVD. Limitations of this study include inability to assess the duration and severity of illness over time. Despite the low prevalence of participants with a history of CVD across states, it is recommended that practitioners educate patients with CVD on the importance of engaging in higher levels of physical activity because of its relationship to general health.

Sponsor: N/A

IRB/IACUC#: 2017-070
An Unusual Case of a Large Left Ventricle Thrombus Presenting as NSTEMI

Background:

Although not common, the Left Ventricle (LV) thrombus can occur within 24 hours post myocardial infarction. Visser et al., showed that about 90% of thrombi are formed at maximum of 2 weeks after the event but can occur as late as 3 months to one year. Thrombus occurs most often with ST-elevation myocardial infarction and it seems to disappear more often in patients with apical akinesia than those with apical aneurysm or dyskinesia. Here we present a case of a large free flowing LV thrombus presenting as an NSTEMI from embolization.

Case Report:

A 56-year-old Hispanic male with PMHx significant for prosthetic aortic valve replacement, permanent pacemaker, paroxysmal A-fib on coumadin, bilateral femoral arteries thrombectomy, heart failure, HTN was brought in by ambulance for retrosternal chest pain (CP) radiating to the left arm. CP was associated with SOB, nausea, headache. Patient underwent cholecystectomy and appendectomy 2 weeks ago. His family reports that Coumadin was stopped during the admission process and was not restarted. The rest of the review of systems was noncontributory except for recent lower extremity edema. Physical exam was significant for lower extremity edema and positional SOB that was worse with the patient lying down and improved with him sitting up in a very specific position. Cardiac exam was WNL, no S3, S4 noted. During the initial work-up it was noted: BUN is 54, creatinine 1.51. Troponin 0.11. EKG with paced rhythm. The patient was diagnosed with acute kidney injury and NSTEMI. Due to persistent chest pain he was taken to the catheterization lab where he was found to have occluded, PDA and PLV and 85% occlusion of PDA branch with clot, underwent successful manual thrombectomy and PTCA. Due to the clot burden cardiology suspected possible origin of thrombus to be of intracardiac origin.

Echocardiogram was ordered an extremely impressive echodense mass was noted. This was 5x5 centimeters with a remarkable and dramatic movement in the left ventricle. It was mostly considered to be a large mural clot. Right and left ventricular function was severely impaired. Cardiothoracic surgery and Interventional Radiology were unable to assist with removing the clot. Palliative services assisted with placing the patient on hospice.

Discussion/Conclusion:

Would like to have the opportunity to share this case with our colleagues due to the staggering echo imaging, the impressive positional SOB that show one more time that a good history and a physical exam are very important for reaching the appropriate diagnosis, and last but not the least due to the extremely difficult treatment option and ethical challenges in patient like this with severe comorbidities.
Peripartum Cardiomyopathy in Neuroblastoma Patient. Pregnancy alone vs Chemotherapy

Background/Abstract:

Although known for decades, etiology for peripartum cardiomyopathy (PPCM) is still eluding. It’s not only a challenging disease for physician but also for the patients due to it’s complexity in management and very high recurrence rate with subsequent pregnancies. Several risk factors for PPCM include: age > 30, multiparity, eclampsia, pre-eclampsia, and prolonged tocolytic therapy with beta agonists. Here we present a case of a young caucasian woman with history of neuroblastoma that developed severe peripartum cardiomyopathy leading to cardiac cirrhosis.

Case Report:

This is a 22-year-old Caucasian female with past medical history of fetal alcohol syndrome, neuroblastoma at birth status post chemotherapy, portal hypertension status post banding, and recently diagnosed peripartum cardiomyopathy. The patient’s pregnancy was complicated with eclampsia, which resulted in a C-Section emergent birth. 2 weeks after birth, patient started complaining of dyspnea on exertion, productive cough with clear sputum, orthopnea and lower extremity swelling. Initial workup with CXR revealed pulmonary vascular congestion, a TTE with EF 5-10%, diffuse hypokinesis, grade 3 diastolic dysfunction, and pulmonary artery peak pressure of 35-40 mmHg, physical examination revealed: pulmonary rales, 2+ pitting LE edema, dyspnea on exertion. Patient was diagnosed with CHF at the time and discharged on Carvedilol and Furosemide; however, 2 weeks later her LE edema continued, this time presenting with worsening dyspnea and tachycardia. Bilateral LE duplex was negative for DVT, but a CTA Chest with contrast revealed a PE in subsegmental Left Lower lobe for which she was started on Apixaban. Her EF remained the same. CHF medications were optimized with Lisinopril, Metoprolol Succinate, Lasix, and Digoxin. Initial hypercoagulable workup was negative, however, the CTA Chest revealed liver lesions. MRI of abdomen revealed a cirrhotic liver secondary to combination of hepatic venous congestion from RHF, chronic portal vein thrombosis, portal hypertension, gastrohepatic varices. The patient’s current therapy for her CHF is: Digoxin, Furosemide, Betablockers, and Milrinone drip. She will be sent for evaluation for liver and heart transplant.

Discussion/Conclusion:

PPCM is a rare but serious condition with high maternal and fetal morbidity and mortality. It is idiopathic but many theories implicate potential role of maternal or fetal hormones, immunological, genetic or environmental factors. Early diagnosis is paramount with strong clinical suspicion, lab markers and echocardiography. Management includes treating heart failure symptomatically as well as potential use of newer therapies targeting immunological system as well as anti prolactin therapy with Bromocriptine and in severe cases cardiac transplant. However, no randomized clinical studies are available till date to support newer therapies. Some questions that we proposed during literature reviews are: is there an
early lab or imaging marker (either maternal or fetal) that can predict PPCM and thus prevent or slow the severity. More studies are needed to answer these puzzling questions.

Sponsor: N/A
IRB/IACUC#: MCFW-IRB
Are waist circumference, sagittal abdominal diameter, and waist-to-height ratio better predictors of cardiovascular risk than BMI?

Purpose: Diseases of the heart are the leading causes of death in the US for adults. Obesity, having excess body fat, is one of the major risk factors for heart diseases. Body mass index (BMI) is one of the popular surrogate measures of excess body fat, and it is established as a predictor of cardiovascular risk. However, ethnicity, age, and sex may also influence the association of BMI and excess fat. While abdominal obesity is associated with metabolic syndrome (a composite risk factor for heart disease), BMI does not account abdominal fat; rather it accounts for the overall excess fat. The purpose of this study was to evaluate waist circumference, sagittal abdominal diameter, and waist-to-hip ratio as surrogate measures of abdominal obesity, and compare their performance with BMI as a predictor of heart disease risk.

Methods: We used data from National Health and Nutrition Examination Survey (NHANES) 2013-2014 for this study. A total of 5,033 adult subjects (mean age 50.85 years and 54% female) participated the survey. We used high-density lipoprotein (HDL) as a risk factor for heart diseases. Univariate analyses were carried out to assess the strength of association between HDL and waist circumference, sagittal abdominal diameter, waist-to-hip ratio, and BMI. We will estimate the strength of different body fat measures separately to predict the heart disease risk (HDL<40mg/dL) using logistic regression, after adjusting for other variables (such as demographic and socioeconomic variables, diet, physical exercise). Finally, we will compare the four body fat measures to find the superior predictor of low HDL.

Results: Average HDL was 52.79 mg/dL and nearly one-fifth of the participants were at risk of heart diseases (HDL/dL). Average BMI, waist circumference and sagittal abdominal diameter were 29.05 kg/m², 98.93 cm, 22.65 cm, respectively. Our preliminary, unadjusted and unweighted, findings suggested that sagittal abdominal diameter was a slightly better predictor of low HDL than waist circumference and BMI; Pearson correlation coefficients were -0.35, -0.34, and -0.27, respectively. We will further estimate the predictability of waist circumference, sagittal abdominal diameter, waist-to-height ratio, and BMI using logistic regression after adjusting for demographic and socioeconomic status.

Conclusions: Findings of this study will help health practitioners to use a better predictor to screen people who are at risk of heart diseases.

Sponsor: N/A
IRB/IACUC#: 2017-104
Interventions for Peripheral Arterial Disease: A Systematic Review

Purpose: Peripheral Artery Disease (PAD), affecting 1 in 5 older adults, impacts blood flow to the lower extremities causing cramping or claudication that potentially limits walking, cardiorespiratory response, muscle performance, and quality of life. The purpose of this systematic review is to investigate interventions effective in improving function in individuals with PAD and its presenting symptoms.

Subjects: Studies reviewed n=21 included Randomized Controlled Trials (RCT’s) and Systematic Reviews (SR’s) with a total of 6,195 subjects ages 60 to 84. For the studies that included the specific subject demographics, there were 3,355 men and 2,202 women with and/or without intermittent claudication.

Methods: Literature search was performed on two databases (PubMed and Cochrane Reviews) for randomized controlled trials (RCT’s) and systematic reviews (SR’s) published between 2010 and 2017, using the following search terms: “interventions,” “resistance training,” “strength training,” “treadmill walking,” “intensive walking,” “aquatic therapy,” “ergometry,” and “blood flow restriction” or “BFR” and PAD. Inclusion criteria for study selection included sample size >20, any language that is translated in English, subjects with an Ankle Brachial Index (ABI)

Data Analysis: The full review of articles was completed by two independent reviewers.

Results: Of the 21 studies reviewed 12 RCT’s and 9 SR’s used the following interventions: comparison studies (n=7 studies); resistance training (n= 2 studies), supervised or conventional exercise (n=5 studies), intensive walking programs (n=1 studies), home exercise programs (n=4 studies), and BFR (n=2 studies) in patients with PAD. Outcomes measured to determine the effects of interventions include: Walking Impairment Questionnaire (WIQ), 6MWT, SF-36, time to claudication, maximal walking distance, and aerobic capacity. Of the interventions, standard walking programs, are most effective at improving walking time and distance, time to claudication, 6MWD, Walking Impairment Questionnaire (WIQ), and quality of life (3,4,5,6,7,9,10,11,17). Resistance training has proved to be as effective, if not more effective than walking (8,12,14,16,17,18) using the same outcomes. Other interventions reviewed showed statistically significant outcomes, and may also serve as complimentary or alternative treatments for individuals with PAD (1,2,14). Future research can look into the effects of BFR for PAD, as it has been shown to improve muscle performance in older adults, without having an impact on arterial stiffness (19,20).

Conclusion: Although methodologies and interventions widely vary, traditional walking programs are considered the gold standard for improved outcomes for individuals with PAD, however, resistance training is just as effective or better in improving the same outcomes and can serve as a component of or alternative intervention (8,12,14,16,17,18). Cycling, home exercise programs, and walking with poles are other interventions that improved outcomes. Interpretation of the results should take into consideration the following limitations: lack of heterogeneity/homogeneity, subject compliance, lack of standardized interventions across the studies, and presence multi-morbidities.
Clinical Relevance: The interventions reviewed are effective in improving outcomes in PAD and are more cost effective than surgical interventions. The presence of comorbidities (i.e. diabetes or other cardiovascular conditions) may attenuate the improvement of symptoms (1,2,15,21) and need to be taken into consideration when measuring exercise tolerance.

**Sponsor:** N/A

**IRB/IACUC#:** N/A
Neurons in the Nucleus Tractus Solitarius show no discernable change in intracellular calcium during acute application of 17\(\beta\)-estradiol

Purpose: Neurons in the Nucleus Tractus Solitarius (NTS) are important regulators of cardiovascular and hormonal responses to stress and a potential site for estrogen modulation of stress responses. Our goal was to elucidate whether acute estrogen receptor activation is associated changes in intracellular calcium in NTS neurons in male and female rats.

Methods: Adult male and female Sprague-Dawley rats were anesthetized with isoflurane and the hindbrain removed and cut into 300um thick sections. The NTS slices were then incubated for 50min with 10\(\mu\)M of Fura-2AM, 0.1% F-127 at 40°C and then washed for 20min in aCSF gassed with 95%O\(_2\)+5%CO\(_2\). A single slice was transferred to the recording chamber on an upright epi-fluorescent microscope. The slice was held in place with a nylon mesh and superfused with normal aCSF at a rate of 2.5 ml/min. Application of 100 nM 17\(\beta\)-estradiol or 63 mM KCl dissolved in aCSF solution was done using multi barrel patch pipette positioned close to the neuron so that injection (volume) occurred in the same direction as the flow of aCSF being perfused. Fluorescence of Fura-2AM was excited by epi-illumination with light provided by a 75 W Xenon lamp band-pass filtered alternatively at 340 or 380 nm. Emission light pass through a barrier filter (510 nm). Pairs of 340 and 380 nm images were acquired at intervals of 5s and analyzed off-line with NIS-Elements AR 3.2 software. All images were captured with a charge-coupled device (CCD) camera.

Results: A total of 19 sections were examined from 4 female rats and an average of 7 cells/slice were analyzed in each section. In response to superfusion of the slice with 100 nM 17\(\beta\)-estradiol no discernable change in the 340/380 ratio was observed in any cell. In 58 neurons from 10 slices in an additional 2 rats, a higher concentration of 1mM 17\(\beta\)-estradiol still failed to alter the 340/380 ratio. Cell viability was confirmed by application of 63 mM KCl which induced a 14 ± 5.4% increase in the 340/380 ratio relative to baseline in the cells studied.

Conclusions: Acute application of 17\(\beta\)-estradiol did not alter intracellular calcium in NTS neurons. This could reflect a true lack of coupling between estrogen receptors and calcium signaling mechanisms in NTS neurons. However, if estrogen receptors are on a subset of NTS neurons, perhaps the fura-2 did not label the relevant population of NTS neurons. Further, perhaps estrogen does not have an acute (non-genomic, membrane bound receptor) effect in NTS and a more prolonged application of 17\(\beta\)-estradiol.

Sponsor: PO1 HL-088052
IRB/IACUC#: 2017-0011
Estrogen Receptor Alpha on Catecholaminergic Neurons in the Nucleus Tractus Solitarius

Purpose: Catecholaminergic neurons in the Nucleus Tractus Solitarius (NTS) are involved in Hypothalamic-Pituitary-Adrenal (HPA) axis and cardiovascular response to stress. While many studies have shown that pre-menopausal females are protected against the hypertensive and sympatho-excitatory effects of stress, very little is known about the location of neurons expressing estrogen receptors within the NTS. Our goal was to elucidate whether estrogen receptor alpha (ERα) is expressed on catecholaminergic neurons in the NTS in male and female rats.

Methods: Adult male and female Sprague-Dawley rats were transcardially perfused with 4% paraformaldehyde and hindbrains harvested. In coronal sections containing the NTS (40um thick) immunohistochemistry was performed to determine whether NTS catecholaminergic neurons express ERα using monoclonal anti-tyrosine hydroxylase (TH) antibody (1:1000, Millipore) and secondary antibody Alexa Fluor 488 donkey anti-mouse (1:500, Jackson ImmunoResearch) and polyclonal anti-ERα antibody (1:2000-5000, Millipore) and secondary antibody Cy3 donkey anti-rabbit (1:400, Jackson ImmunoResearch). Sections were captured using an Olympus BX41 Fluorescence Microscope and analyzed using ImageJ. The NTS was divided into 2 regions: sections caudal to the area postrema (caudal CAUD) and sections lying below the area postrema (sub-postrema SP), and the number of immunoreactive neurons in each region counted and expressed as an average number of labeled neurons per section±SEM. The number of sections analyzed ranged from 7-11 in CAUD and 3-7 in SP.

Results: In male rats, TH in CAUD NTS (n=6) was observed in 26±4 and ERα in 24±4 neurons/section. Co-localization of ERα and TH was observed in 13±2 neurons/section. TH in SP NTS (n=5) was observed in 54±3 and ERα in 34±2 neurons/section. Co-localization of ERα and TH was observed in 15±2 neurons/section. In female rats, TH in CAUD NTS (n=6) was observed in 27±2 and ERα in 30±3 neurons/section. Co-localization of ERα and TH was observed in 17±2 neurons/section. TH in SP NTS (n=6) was observed in 50±4 and ERα in 52±5 neurons/section. Co-localization of ERα and TH was observed in 27±2 neurons/section. At sacrifice, females were in estrus (1), diestrus (2) or proestrus (3).

Conclusions: In both males and females, ERα is expressed on a subset of catecholaminergic NTS neurons, as well as non-catecholaminergic neurons. This could provide a substrate for estrogen-mediated cardiovascular protection in females.

Sponsor: PO1 HL088052
IRB/IACUC#: IACUC-2017-0011
An Unusual Case of Viral Cardiomyopathy Presenting as Acute Ischemic CVA

Background/Abstract:

HIV-associated cardiomyopathy (HIVAC) is a significant cause of morbidity and mortality among HIV-infected individuals. The HIV virus is increasingly becoming recognized as an important cause of cardiomyopathy. While the exact mechanism remains unclear, effects from direct viral burden as well as opportunistic infections are thought to play a key role. Here we present a case of severe cardiomyopathy in a patient previously undiagnosed with HIV.

Case Report:

A 21yo Hispanic male with PMH significant for fatty liver disease and recent Tylenol toxicity presented to the ER for evaluation of sudden onset of left sided weakness and left facial droop. He was found down and noted to be shaking, thus there was also a concern for seizure activity. NIHSS upon arrival was 16, with early changes on CT and visualized clot in M1 distribution of the right MCA with poor collateral flow on CTA. Right MCA syndrome was diagnosed and patient was given tPA. Patient recovered well with rapid resolution of the focal deficits. Prothrombotic workup revealed low protein C activity. Transthoracic echo performed as part of evaluation of ischemic CVA demonstrated a LVEF of 15% and moderately dilated left ventricle. The etiology of CVA was felt to be thromboembolic secondary to this severe cardiomyopathy. Patient denied any personal or family history of prior cardiac problems as well as cardiac arrhythmias. Due to noted recurrent fevers and pancytopenia throughout the course of his admission, HIV reactivity was checked and revealed him to not only have HIV but also AIDS with a CD4 count of 84 and RNA PCR of 121,000. With this finding, viral cardiomyopathy was felt to be the most reasonable explanation for heart failure in this young patient. He was started on oral anticoagulation to prevent further thromboembolic events and was fitted for a LifeVest.

Discussion/Conclusion:

HIV-associated cardiomyopathy is a known chronic complication in patients living with HIV/AIDS, especially in uncontrolled infection as was seen in the patient who presented to our hospital. Uncontrolled infection can lead to both direct and indirect cardiotoxicity from infections associated with low CD4 counts as well as HIV itself. The pathogenesis of HIV-induced cardiomyopathy is often multifactorial including myocarditis, cardiac autoimmunity, micronutrient deficiency, and even antiretroviral therapy (ART) induced. Patients living with HIV are at a higher risk than the general population for developing HF. Studies have shown that in HIV-infected individuals, the prevalence of HF was highest among those with CD4 counts

Sponsor: N/A
IRB/IACUC#: MCFW-IRB
6-Hydroxydopamine Aggravates Renal Injury and Inflammation in a Murine Model of Systemic Lupus Erythematosus

Purpose: Renal inflammation is prevalent in the chronic autoimmune disease systemic lupus erythematosus (SLE) and drives the progression of kidney injury. Inflammation in SLE results from a loss of self-tolerance and the production of autoantibodies against nuclear antigens. However, other immunoregulatory mechanisms, such as the cholinergic anti-inflammatory pathway, may also be dysregulated and contribute to aberrant systemic and renal inflammation in the disease. The cholinergic anti-inflammatory pathway is a protective, neuroimmune mechanism thought to involve neurotransmission between the parasympathetic vagus and the sympathetic splenic nerves. In order to confirm the importance of the splenic nerve in this pathway, others have used 6-hydroxydopamine (6OHDA), a neurotoxin that depletes catecholamines, to chemically denervate the spleen and thereby dampen the sympathetic component of the cholinergic anti-inflammatory pathway. We hypothesized that splenic injection of 6OHDA would further disrupt the cholinergic anti-inflammatory pathway in a mouse model of SLE and result in increased renal inflammation and worsened disease severity, which would highlight the importance of the splenic nerve in quelling renal inflammation.

Methods: In the current study, female SLE and control mice were injected with 6OHDA (120 µg in 60 µl saline) or vehicle directly into the spleen at 33 weeks of age (n = 6/group). To confirm splenic denervation with 6OHDA, we utilized the glyoxylic acid condensation reaction on 12 µm spleen sections of representative animals and verified that catecholamine histofluorescence was diminished in 6OHDA-treated mice (205 vs. 111 histofluorescent foci).

Results: Renal cortical TNF-α (normalized to total protein) was increased in SLE mice compared to controls (3.1e6 ± 1.2e5 vs. 7.8e5 ± 1.6e4 intensity units; p = 0.029), and 6OHDA exacerbated this pro-inflammatory cytokine in SLE mice (7.6e6 ± 2.4 intensity units; p = 0.048) with no effect in controls (2.4e6 ± 6.6e5 intensity units; p = 0.697). Anti-dsDNA autoantibodies were elevated in SLE mice compared to controls (2.1e4 ± 5.7e3 vs. 1.0e4 ± 4.7e3 activity units; p = 0.013), but 6OHDA did not alter this measure of disease severity in SLE mice (1.8e4 ± 5.2e3 activity units; p = 0.692). Albumin excretion rate (AER) was elevated in SLE mice compared to controls (160.7 ± 28.0 vs. 2.7 ± 2.7 mg/dL; p < 0.001). 6OHDA accentuated the increase in AER in SLE mice (454.2 ± 150.2 mg/dL; p = 0.010) but had no effect in controls (27.5 ± 17.0 mg/dL; p = 0.754).

Conclusions: In summary, 6OHDA aggravated renal inflammation and injury in SLE mice indicated by heightened renal cortical TNF-α and AER. This suggests that chemical splenic denervation may disrupt endogenous, sympathetically-mediated anti-inflammatory mechanisms. Further studies are needed to confirm the role of the splenic nerve in regulating renal inflammation.

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IRB/IACUC#: IACUC-2017-0033
Effect of General Anesthesia on Cardiac Magnetic Resonance Derived Cardiac Function in Tetralogy of Fallot.

Introduction: Surgical palliation of tetralogy of Fallot (TOF) results in excellent short-term survival, however, residual defects result in increased long-term mortality. Depressed right ventricular (RV) and left ventricular (LV) ejection fractions (EF) are associated with adverse outcomes. While cardiac magnetic resonance (CMR) imaging is the preferred modality to assess these patients, some require sedation for successful data acquisition. General anesthesia (GA) has been shown to depress EF and heart rate (HR) in animal models. The effect in patients with congenital heart disease has not been well described.

Case Information: A retrospective review was conducted of all CMR patients referred with TOF between January 2011, and May 2017. Patients with significant aortic or mitral valve disease, history of cardiomyopathy, undergoing conscious sedation, or receiving inotropic support were excluded. The cohort was separated into GA and non-sedated groups. A standard anesthetic regimen using sevoflurane was used in all patients. Propensity score matching (PSM) was utilized to adjust for selection bias. The matching algorithm was used in matched subjects to calculate the mean differences in LVEF, RVEF, HR, and cardiac index (CI). A total of 114 patients met criteria, 31 patients were administered GA (mean age 15 years, range 2 – 45, 48% male), while 83 patients received no sedation (mean age 19 years, range 11 – 53, 53% male). The unmatched analysis showed significant depression in LVEF (49.9 vs 56.8%, p

Conclusions: GA with sevoflurane results in myocardial depression and significantly depressed CMR derived LVEF, RVEF, and CI. It may be inappropriate to use this data to determine surgical timing for pulmonary valve replacement. Studies examining the effect of GA and the use of alternative protocols should be conducted.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Outcomes of Hypoplastic Left Heart Syndrome with and without Restrictive Atrial Septum

Introduction: Hypoplastic Left Heart Syndrome (HLHS) is a congenital heart defect characterized by inadequate development of a functional left ventricle to the point where it is unable to support systemic circulation. Patients often undergo a series of palliative surgeries beginning with the Norwood procedure within several weeks of life, which has greatly improved the mortality rate associated with this condition. However, about 6-22% of these patients also have an intact atrial septum (IAS) or restrictive atrial septum (RAS), which is associated with significantly worse survival rates. Multiple strategies have been developed in order to treat this complication. The Cook Children’s Heart Center tends to perform early Norwood procedures (day 0-1 of life), and one of the goals of this study is to analyze the outcomes of performing early Norwood procedures. It was hypothesized that the Cook Children’s institutional approach of early Norwood procedure for patients with HLHS with RAS is at least comparable, if not superior, to other approaches in terms of survival and long term outcomes.

Methods: This was a retrospective study of patients who had a Norwood procedure done at Cook Children’s Hospital from 2014 – 2016; 36 patients met inclusion criteria. Data were collected for variables of significance, including presence of restrictive atrial septal defect (ASD), pre- vs. post-natal diagnosis of HLHS, survival to discharge, and mortality. Using logistic regressions, we examined the effect of ASD and pre- vs. post-natal diagnosis on survival at discharge, and overall mortality.

Results: Thirty-one of 36 (86%) patients survived. Those with ASD (4/6) were not statistically significantly less likely to survive than those without ASD (27/30), p=.13, and those born pre-natally (23/26) were not significantly less likely to survive than those born post-natally (8/10), p=.51.

Discussion: The survival rates at discharge were slightly higher than published survival rates for patients with and without restrictive ASD. While the results are preliminary, and further research with a larger sample size is needed, we believe our current data shows a trend that supports our hypothesis.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Canonical Wnt signaling in optic nerve head

Purpose: While canonical Wnt signaling has been explored in areas of the eye like the trabecular meshwork and ciliary body during glaucomatous pathology, it has not been explored in the lamina cribrosa. Complement protein 1, subunit q (C1q) has been shown to be an activator of the canonical Wnt pathway leading to an increase in fibrosis in various tissues, but not explored in the lamina cribrosa (LC) either. As C1q concentration increases in blood serum and central nervous system with an increase in age, C1q activation of canonical Wnt signaling may be an important factor in glaucomatous pathology. Therefore, we aimed to prove that a functional canonical Wnt signaling pathway is expressed in the lamina cribrosa and that C1q is an activator of the pathway.

Methods: Primary mouse optic nerve head (ONH) astrocytes from C57BL/6J mice were cultured and characterized. When confluent, cells were serum starved overnight and then treated for 24 hours with 100 nM Wnt3a or left untreated as a control. Following treatment, cells were collected and had cytosolic and nuclear fractions separated. Fractions were then western blotted and probed for β-Catenin. Bands were analyzed via densotometry and fold changes in expression were compared to control cells.

Results: In a single primary mouse ONH astrocyte cell strain, β-Catenin expression increased 1.354-fold when treated with 100 nM Wnt3a compared to control in the cytosolic fraction and 1.145-fold when treated with 100 nM Wnt3a compared to control in the nuclear fraction. Without additional cell strains, statistical significance is not able to be determined.

Conclusions: Our very preliminary results support our hypothesis that a functional canonical Wnt signaling pathway is expressed in the LC. Additional cell strains will need to be examined to fully determine presence of a functional canonical Wnt signaling pathway as well as determining if C1q activates the pathway in this population.

Sponsor: T32 AG020494
IRB/IACUC#: N/A
TARGETING ASTROGLIOSIS DURING METH AND HIV-1 EXPOSURE

Purpose: As a popular psychostimulant, methamphetamine (METH) use leads to long-lasting, strong euphoric effects. METH exacerbates the severity and onset of HIV-associated neurocognitive disorders (HAND), which affect 30-70% of the 37.6 million people globally infected with HIV. Most neurodegenerative diseases share neuroinflammation as a common pathogenic mechanism. Neuroinflammation, HIV and METH dysregulate a wide range of brain functions including neuronal signaling, glial activation, viral infection, oxidative stress and excitotoxicity. Since neuroglia often determine the outcomes of neurological disease, we investigated the mechanisms regulating astrocyte-mediated neurotoxicity in the context of METH and HIV comorbidity.

Methods: To these ends, we examined the expression, localization and function of the novel METH astrocyte receptor, trace amine associated receptor 1 (TAAR1) in an in vitro model of HIV-associated activation wherein extended METH exposure is administered to mimic residual METH concentrations that occur in humans between binges of METH-taking.

Results: In this model, TAAR1 levels, and its localization to the endoplasmic reticulum (ER) and plasma membranes, increased with METH and HIV-induced astrogliosis. Calcium flux, which mediates ER, mitochondrial, and oxidative stress, also was increased, corroborating our prior studies on astrocyte mitochondrial dysregulation. The astrocyte responses to METH and HIV-relevant stimuli were blocked with the TAAR1-selective antagonist EPPTB. Extended METH and HIV activation impaired excitatory amino acid transporter 2 (EAAT2) expression and activity, which were recovered by following 24 hour exposure with EPPTB.

Conclusion: Together, these data highlight several mechanisms regulating METH/HIV-induced, astroglia-mediated neurotoxicity and the potential for astrocyte targeted intervention via TAAR1 during chronic disease.

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IRB/IACUC#: 2007-121
Targeting Astrocyte HIV-1 Proviral Reservoirs in HAND

Purpose: Although antiretroviral therapy (ART) has greatly reduced the incidence of HIV-associated dementia (HAD), nearly 50-70% of HIV-1 infected individuals develop HIV-associated neurocognitive disorders (HAND). Between 5-20% of astrocytes harbor HIV-1 provirus, and they do not actively propagate viral infection. However, it is well established that astrocytes produce viral proteins, which cause changes in astrocyte function and aggravate HAND pathogenesis. Moreover, in vivo it is difficult to distinguish latently infected astrocytes from healthy cells. Thus, there is a great need to identify latently infected astrocytes and develop strategies to target this specific population. We hypothesize that HIV-1 proviral reservoirs alter astrocyte function and gene expression patterns, which could serve as biomarkers to facilitate targeted therapy.

Methods: The dual-labeled, fluorescent reporter Red/Green-HIV-1 (R/G-HIV-1) was used to visualize viral promoter (LTR) activity in primary human astrocytes. Astrocytes were spinoculated with pseudotyped R/G-HIV-1-WT. Exposed uninfected (R-/G-), astrocytes with active (R+/G+) and silent (R+/G-) LTRs were enriched using fluorescence activated cell sorting (FACS). Subsequently, these cells were used to evaluate viral protein expression, functional studies, and preliminary RNA sequencing.

Results: Astrocytes with silent viral promoter are devoid of late viral proteins such as p24, indicating a functionally silent HIV-1 LTR. Vorinostat, an HDAC inhibitor, reactivated silent HIV-1 LTR in R/G-HIV-1-infected astrocytes. Preliminary data indicate that astrocytes with silent (R+/G-) and active (R+/G+) LTRs have significantly impaired glutamate clearance ability and cell proliferation compared to exposed uninfected (R-/G-) cells. Interleukin-1β (IL-1β) a HAND relevant stimuli, further reduced glutamate clearance ability of these independent populations. However, harboring the HIV-1 provirus did not alter inflammatory responses of astrocytes, such as CXCL8 and CCL2 production, either alone or in presence of IL-1β.

Conclusions: Our data suggest that harboring HIV-1 provirus with either active or silent viral promoters interfered with astrocyte function and growth. Hence, we propose that identifying biomarkers for astrocytes harboring HIV provirus, and therapeutic gene editing to eliminate proviral gene expression, will improve physiological function compared to HIV-1 infected cells.

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IRB/IACUC#: 2007-121
Polymeric Nanoparticle-Mediated GFAP-TIMP-1 Gene Delivery to Human Astrocytes

Purpose: The neuroprotective functions of astrocyte tissue inhibitor of metalloproteinases-1 (TIMP-1) during HIV-1-induced apoptosis are documented. However, astrocyte TIMP-1 levels decrease during chronic inflammation typical of HIV-associated neurocognitive disorders (HAND). We hypothesize that nanoparticle (NPs) mediated, astrocyte-targeted TIMP-1-gene delivery could restore TIMP-1 levels and serve as a HAND therapy. Optimally biocompatible polymeric NPs with validated in vivo reporter gene expression would serve as gene delivery vehicles. TIMP-1 overexpression may be restricted to astrocytes, using a glial fibrillary acidic protein (GFAP) promoter-driven gene expression, without adversely affecting the astrocyte structure and functions.

Methods: We tested biocompatibility, dose-time kinetics, and in vivo gene delivery with arginine-modified polyethylenimine (PEI) analogs (AnPn) in vitro (primary human neural cells) and in vivo (mice) using a cytomegalovirus (CMV) promoter-driven luciferase plasmid (pLuc). Truncated and full-length GFAP promoter-driven plasmids encoding luciferase-reporter (gfa-Luc) and TIMP-1 (gfa-TIMP-1) were sub-cloned. Astrocytes transfected with AnPn-delivered gfa-Luc and gfa-TIMP-1 were evaluated for morphological changes, inflammatory biomarker profiles, and glutamate clearance to evaluate if critical astrocyte functions are affected.

Results: Select PEI analogs (AnPn) led to robust and sustained reporter gene expression in astrocytes. Successful in vivo reporter gene delivery to the brain was confirmed by luminescence assay and immunohistochemistry. Truncated GFAP promoters led to a detectable gene expression in astrocytes compared to full-length GFAP promoters, which was regulated by inflammatory stimuli. Lastly, gfa-TIMP-1 plasmids were successfully delivered using AnPn to astrocytes in the presence and absence of HIV-relevant stimuli. Immunocytochemistry, and proinflammatory biomarker profiles of transfected astrocytes were analyzed to delineate NP-specific versus TIMP-1-specific changes.

Conclusions: These studies confirmed successful polymeric NPs-mediated reporter gene delivery in vitro and in vivo. Subsequently, NPs-mediated GFAP promoter-driven reporter and TIMP-1 gene expression was demonstrated in vitro. These findings serve as proof-of-concept towards testing therapeutic TIMP-1 gene delivery and demand future investigations geared towards clinical translations for HAND treatment.

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IRB/IACUC#: 2007-121; 2017-0017
**miR-200b-3p and miR-211-5p downregulate the expression of extracellular matrix and associated proteins in human optic nerve head astrocytes**

**PURPOSE:** microRNAs (miRNAs) are a class of small, endogenous non-coding RNAs that epigenetically regulate post-transcriptional gene expression. miRNAs are known to modulate cellular functions such as extracellular matrix (ECM) turnover. There is evidence that dysregulation of miRNA expression has a role in the pathogenesis of fibrotic diseases including glaucoma. Glaucoma is a leading cause of irreversible blindness and is associated with fibrotic changes to the optic nerve head (ONH), the initial site of glaucomatous damage to the retina and optic nerve. Our previous study showed that expression of the profibrotic cytokine TGFβ2 is elevated in the ONH of glaucoma eyes compared to age-matched normal eyes. Currently there is a lack of knowledge regarding the roles of miRNAs in the ONH. The purpose of this study was to determine: (a) differences in the expression of profibrotic and anti-fibrotic miRNAs in normal ONH astrocytes treated with or without TGFβ2 and (b) whether candidate miRNAs (miR-200b-3p and miR-211-5p) regulate the expression of ECM and ECM associated proteins in the ONH.

**METHODS:** Primary normal human ONH astrocytes (ONA) were grown to 100% confluency. ONA were treated with 5ng/ml TGFβ2 or with control for 24hrs. miRNA qPCR arrays were performed to compare the expression levels of profibrotic and anti-fibrotic miRNAs in normal ONA treated with or without TGFβ2. ONA were transfected with miR-200b-3p and miR-211-5p mimics at 10nM, 5nM, and 1nM concentrations to confirm target predictions based on the TargetScan database. An all stars negative control siRNA was included which will not recognise any mammalian gene.

**RESULTS:** The miRNA qPCR arrays analysed from normal ONA exposed to TGFβ2 showed that TGFβ2 downregulated the expression of hsa-miR-200b-3p and hsa-miR-211-5p. Transfection of miR-200b-3p mim downregulated fibronectin (FN), gremlin, and tissue transglutaminase II in ONA. Transfection of miR-211-5p downregulated FN and gremlin in ONA.

**CONCLUSIONS:** Our results suggest that TGFβ2, which is elevated in the glaucomatous ONH, modulates the expression of miRNAs in ONA. These miRNAs target FN, TGM2, and gremlin to modify the ECM in the ONH. Downregulation of anti-fibrotic miRNAs may contribute to fibrosis of the ONH.

**Sponsor:** RP20022 and T32 AG020494

**IRB/IACUC#:** N/A
Elucidating molecular mechanisms of TAAR1-dependent astrocyte regulation during HIV-associated neurocognitive disorders and methamphetamine exposure

Purpose: A study conducted in 2012 estimated that 1.2 million people in the U.S. reported the use of methamphetamine (METH) in the previous year, with 133,000 new users age 12 or older. METH is a highly addictive substance that leads to an imbalance in dopamine and norepinephrine release causing euphoric effects. Long term METH use has been linked to many central nervous system (CNS) abnormalities including deficits in memory, executive function, anxiety and depression. METH use is associated with risky sexual behavior, lowered inhibitions and increased likelihood for acquiring HIV. METH abuse exacerbates the onset of HIV-associated neurocognitive disorders (HAND) and promotes a neurotoxic environment by increasing oxidative stress and excitotoxicity. Our lab previously identified trace amine associated receptor 1 (TAAR1) as a novel stimulatory G protein coupled receptor in primary human astrocytes. The expression of TAAR1 is modulated by METH and HAND-relevant stimuli. We hypothesize that TAAR1 dysregulates astrocyte intracellular signaling during HAND and METH exposure thus contributing to disease pathogenesis.

Methods: To mimic upregulation of TAAR1 during HIV CNS disease, TAAR1 overexpression was studied in human astrocytes. We then used a physiologically relevant model of extended METH exposure and low level HIV-associated activation. First, exogenous TAAR1 expression and intracellular localization were characterized. Next, TAAR1 localization with HAND relevant stimuli and METH exposure were assessed. Finally, TAAR1-dependent signaling and activation of downstream modulators were evaluated. We used a TAAR1 selective antagonist, EPPTB, to determine TAAR1-dependent changes in astrocyte function.

Results: The overexpression model was standardized for TAAR1 levels in astrocytes. TAAR1 function mirrored expression levels in transfected astrocytes. Exposure to METH and HAND-relevant stimuli altered astrocyte functional responses, including proliferation and reactive morphological phenotype.

Conclusions: Our study aims to delineate therapeutically targetable mechanisms that regulate astrocytes during neuroinflammation in HAND and METH exposure. Therefore, we propose astrocyte TAAR1 as a potential target to combat neurocognitive decline.

Sponsor: NIDA RO1: DA039789
IRB/IACUC#: 2007-121
Silencing Astrocyte Elevated Gene-1 during Calcium Signaling and Glutamate Excitotoxicity

Purpose: During central nervous system (CNS) injury or infection, astrocytes undergo inflammatory and functional changes, ultimately regulating cognitive impairment. Among these devastating changes is the downregulation of excitatory amino acid transporter 2 (EAAT2). EAAT2 is critical for glutamate uptake in synaptic clefts, so when downregulated, results in glutamate excitotoxicity. Our previous studies highlighted astrocyte elevated gene-1 (AEG-1) overexpression as a novel modulator of EAAT2 repression during HIV-1 associated neuroinflammation. Additionally, elevated AEG-1 levels are evident in several cancers, neurodegeneration, oxidative stress, and aging. AEG-1 cooperates in several cell signaling pathways mediating cell development, inflammation, proliferation, differentiation, metabolism, apoptosis, and autophagy. While AEG-1 is ubiquitously expressed, levels are higher in muscle-dominated organs and endocrine glands, suggesting a role of AEG-1 in calcium associated signaling. Furthermore, we have shown AEG-1 to have a direct interaction with the calcium-binding chaperone calnexin. Both calcium and glutamate are prominent CNS signaling molecules reported to be dysregulated during conditions AEG-1 is often upregulated. However, the role of AEG-1 in calcium signaling has not yet been explored.

Materials & Methods: AEG-1 specific siRNA was used to isolate AEG-1 dependent outcomes. Astrocyte activation was measured via morphological staining and cytokine ELISA. EAAT2 protein and mRNA expression were examined in conjunction with functional glutamate clearance assay to correlate potential glutamate excitotoxicity. Calcium signaling was measured by live cell confocal microscopy using a genetically encoded calcium sensor.

Results: AEG-1 siRNA significantly decreased protein and mRNA expression of AEG-1 compared to non-specific siRNA. Preliminary studies for calcium signaling required standardization and suggest a decreased calcium response when AEG-1 is knocked down. Additional investigations are still in progress.

Conclusion: The current study focuses on investigating how AEG-1 regulates calcium signaling and astrocyte activation in connection with glutamate excitotoxicity. These findings will help better understand AEG-1 mediated dysregulation of astrocyte function, possibly identifying a novel therapeutic target for cognitive impairment.

Sponsor: N/A
IRB/IACUC#: 2007-121
Estimated community prevalence of Autism Spectrum Disorder with and without co-occurring Developmental Coordination Disorder significantly exceeds observed prevalence at two Tarrant County sites offering primary and secondary care.

Background: Autism Spectrum Disorder (ASD) can co-occur with Developmental Coordination Disorder (DCD), and ASD+DCD requires integrated care. Cook Children’s Medical Center (CCMC) and the Child Study Center (CSC) are the most comprehensive options for care in Tarrant County, offering integrated developmental pediatrics and secondary ASD services. Lack of integration between primary and secondary services can lead to discontinuity in care or incomplete diagnosis, or prevent families from entering the pathway to ASD-related services altogether.

Objective: Determine whether CCMC and CSC serve a patient population proportional to the estimated prevalence of ASD in Tarrant County. If not, it will highlight a need for more primary care sites with integrated autism services.

Hypothesis: The number of patients with ASD, DCD, and ASD+DCD served by CCMC and CSC will be significantly lower than estimated prevalence in Tarrant County.

Method: This retrospective study evaluated patients who were 0-21 years old at the time of first chart entry, with a diagnosis of ASD, DCD, or ASD+DCD. We compared the observed patient population of ASD, DCD, and ASD+DCD at CCMC and CSC to the expected Tarrant County population.

Results: At current prevalence estimates, the expected population of children in Tarrant County with ASD is 8,078, and with DCD is 37,695. At CCMC, the number of patients since 1994 with ASD was 5,520, with DCD was 424, and with ASD+DCD was 59. At CSC, the number of patients since 1994 with ASD was 1,559, with DCD was 46, and with ASD+DCD was 232. The CCMC EMR contained 32 different diagnostic codes for ASD (e.g., Asperger’s Syndrome, active infantile autism, autistic disorder of childhood onset) and 4 codes for DCD (e.g., dyspraxia, developmental coordination disorder).

Conclusions: The observed number of patients served was disproportionate to the estimated population. Other public agencies serve a small, non-overlapping population with ASD, unlikely to make up the difference between the estimated and observed population. There is a clear gap in the number of patients with ASD, DCD, and ASD+DCD served at integrated care sites. Many children may be (1) undiagnosed, (2) diagnosed but not seeking care in an integrated care site, or (3) inaccurately
diagnosed. Minority groups are at high risk for misdiagnosis; since 41.6% of the Tarrant County population is Black or Hispanic, health disparities may limit their access to comprehensive evaluation and care.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
A multi-center retrospective investigation of diagnostic, referral, and early management pathways for pediatric patients with Autism Spectrum Disorder and Developmental Coordination Disorder.

Background: Autism Spectrum Disorder (ASD) and Developmental Coordination Disorder (DCD) can co-occur, but diagnostic procedures vary widely. Some overlap exists in behavioral, motor, and social problems in ASD and DCD, which adds ambiguity to the diagnostic process. Provider- and patient-centered factors contribute to the differences in pathways to care; understanding these factors may lead to more robust guidelines for assessment of patients with suspected ASD, DCD, and ASD+DCD.

Objective: Measure prevalence and describe the diagnostic pathway of ASD+DCD at 3 healthcare sites, and describe the diagnostic pathways reported for ASD, DCD, and ASD+DCD. Identify provider- and patient-centered variables related to diagnostic, early management, and referral patterns.

Hypothesis: A combination of patient- and provider-centered variables will contribute to differences in diagnostic and management outcomes for patients with ASD, DCD, and ASD+DCD.

Methods: This retrospective study evaluated patients diagnosed with ASD, DCD, and ASD+DCD in the Cook Children’s Medical Center (CCMC) network, UNT Health Science Center (UNTHSC), and the Child Study Center (CSC). Charts included patients ages 0-21 years at the time of first entry, with documented diagnosis of ASD, DCD, or ASD+DCD. We collected primary and co-occurring diagnoses, medications, developmental milestones, test scores, social history, time between first concern visit and diagnosis, and services consulted.

Results: At CCMC, the number of patients with ASD was 5520, with DCD was 424, and ASD+DCD was 59. At CSC the number of patients with ASD is 1559, with DCD is 46, and ASD+DCD, 232. UNTHSC data collection will take place in March 2018. We used a stratified random sample of 50 subjects from each diagnostic group (ASD, DCD, ASD+DCD) for initial analyses. Analyses are ongoing, and include correlations and analyses of variance to identify relationships and group differences among patient- and provider-centered variables.

Conclusion: The number of patients with ASD, DCD, and ASD+DCD served by CCMC and CSC is significantly lower than anticipated given prevalence estimates. ASD+DCD prevalence was higher at CSC than at CCMC. Assessment and diagnostic procedures at CSC are more extensive, and include developmental motor testing. Higher surveillance at this site may explain the higher observed prevalence of ASD+DCD. Further planned analyses will illuminate patient- and provider-centered differences among the 3 groups.
**Sponsor:** N/A

**IRB/IACUC#:** CCHCS-IRB 2017-057 / 2018-024
Microsimulation to determine likely scope of pharmacogenomic testing in a Diabetic Population

Purpose: Despite metformin’s standing as the primary treatment drug for Type 2 Diabetes Mellitus, over one-third of patients on metformin monotherapy fail to achieve glycemic control, and 25% have adverse reactions. Furthermore, within 3 years, 21% start on a second drug, usually a sulfonylurea. While combination therapy is effective, 27.8% of those on sulfonylurea therapy present with hypoglycemic episodes, of which 3.6% are severe, resulting in hospitalization and/or death.

An individual’s genetic makeup plays a role in their body’s ability to utilize drugs, and can affect their chances of developing potential side effects to pharmacotherapy. Pharmacogenomics utilizes a patient’s genome to establish an appropriate therapy or dosing regimen to ensure that treatments work effectively with minimal side effects. This project aims to determine whether utilizing pharmacogenomic variants to tailor drug regimens in individuals with T2DM would have clinical efficacy.

Materials/Methods: We created a model diabetic population using a microsimulation technique based on Tarrant County demographics and allelic variant population frequencies for metformin and sulfonylurea pharmacogenes to determine the frequency of actionable genotypes (variants that play a role in drug pharmacodynamics). Furthermore, we determined whether actionable genotypes varied based on racial/ethnic groups.

Results: Between 20 to 60% of the population had 1 or more actionable genotypes for sulfonylurea drugs, depending on race/ethnicity, with Caucasians presenting with 1 or more actionable genotypes approximately 68% of the time. Caucasians also present with actionable genotypes that affect metformin pharmacodynamics 3% of the time, followed by African Americans presenting with actionable genotypes for metformin 2% of the time. Furthermore, almost 50% of the population has 1 or more actionable genotype for either metformin or sulfonylurea pharmacodynamics.

Conclusions: Oral hypoglycemic drug therapy efficacy and potential failure may be influenced by the genetic prevalence of allelic polymorphisms, and the degree of influence varies by racial/ethnic group. The data derived from these simulations will be used in an adverse drug reaction model to enable us to determine if pharmacogenomics studies will better allow for the control of HbA1c levels in T2DM, thereby decreasing the incidence of diabetic complications and adverse drug reactions.

Sponsor: N/A
IRB/IACUC#: N/A
North Texas Smartphone Contamination Initiative: Proposal to investigate the restroom cellphone use in medical students and healthcare professionals

Situation: Preventable medical errors are the third leading cause of death in the United States annually, accounting for 251,000 lives annually. Healthcare-acquired infections (HAIs) account for nearly 40% of this population, costing the healthcare system $28.4-33.8 billion each year.

Background: The rising prevalence of smartphone use has prompted their investigation as potential vectors for infectious transmission in healthcare. Although sophisticated reference applications may be invaluable to healthcare professionals, these smartphones are easily contaminated and rarely disinfected. One potential source for significant smartphone contamination is use in restrooms. Little empirical research investigated this proposition. However, according to several crowd-sourced population surveys, the pervasiveness of restroom smartphone usage ranges from 61-75%.

Assessment & Proposed Solution: Given the diverse microbial biogeography found in public restrooms, smartphone usage is an alarming health concern. Through targeted surveillance of medical students and healthcare workers, the proposed study will be the first investigate the linkage between restroom smartphone usage and subsequent contamination. We will also follow previously designed protocols demonstrating that bacteria can be aerosolized and contaminate nearby objects, and apply this principle to mobile phones contamination. The results of this study have potential to impact health policy aimed at reducing the spread of HAIs, significantly improving quality and safety for patients nationwide.

Sponsor: N/A
IRB/IACUC#: N/A
Does General Health Differ by Physical Activity Level in Middle Aged Diabetic Females?

Purpose: Diabetes is a widespread health issue in the general population, but limited information is available for the relationship between physical activity level and general health in diabetic patients, especially in specific age or gender subpopulations. The goal of this study was to determine whether general health differs by physical activity level in middle-aged diabetic females.

Methods: This cross-sectional analysis used 2015 BRFSS data for middle-aged diabetic females ages 45-64 from Arkansas, Missouri, Ohio and West Virginia. Multiple logistic regression analysis assessed the relationship between physical activity level and general health while controlling for weight status, health conditions, alcohol use, tobacco use, education level, employment status, age, and ethnicity/race.

Results: Across states, about half of the females ages 45-64 reported having good or better general health (38-52%) and less reported being highly active (16-23%). The results of adjusted analysis indicated good or better general health was significantly related to highly active physical activity level in Ohio (AOR= 3.09, 95%CI= 1.55, 6.15) and Missouri (AOR= 5.72, 95%CI= 1.99-16.80). Additionally, good or better general health was related to employment status in all four states (large effect sizes). In contrast, good or better general health was inversely related to health conditions in two of the four states (large effect sizes).

Conclusions: A highly active physical activity level was found to be significantly related to general health in two out of four states. Since this data was from a population-based study, the results may generalize to middle-aged diabetic females presenting to a general practice clinic. Thus, primary care practitioners can expect to see a low to moderate prevalence of middle-aged diabetic females reporting a highly active physical activity level and good or better general health. Providers should consider assessing the activity level and general health of diabetic middle-aged female patients as well as consider their comorbid health conditions and provide education and resources to encourage physical activity as indicated.
Short term exposure to high glucose negatively regulates store-operated calcium channel proteins in mesangial cells.

Purpose: Glomerular mesangial cells (MCs) are an important target of metabolic abnormalities in diabetic environment. The Orai1-mediated store-operated calcium entry (SOCE) is associated with many physiological processes in a variety of cells, including MCs. However, whether SOCE in MCs is involved in diabetic kidney disease is not clear. High glucose (HG) is the principal cause of MC pathogenesis in diabetes and altered MC function by HG is central to the pathogenesis of progressive diabetic glomerulopathy. The present study was carried out to determine if HG treatment altered the protein content of Orai1 and the protein-mediated SOCE in MCs.

Methods: Western blot was conducted to estimate abundance of Orai1 protein and Fura-2 fluorescence ratiometry was used to analyze SOCE.

Results: We found that treatment of rat MCs with HG (25 mM) for time periods ranging from 2 hours to 24 hours decreased abundance of Orai1 protein. A significant decrease was observed at the time point of 8 hours, which sustained at least for additional 16 hours. Consistently, HG treatment for 8 hours significantly reduced SOCE. HG treatment for the same time periods did not alter the level of Orai1 transcript. In the presence of cycloheximide, a protein synthesis inhibitor, the HG effects on the level of Orai1 protein still existed, suggesting posttranslational mechanisms involved. Furthermore, both MG132 (the ubiquitin-proteasome inhibitor) and NH4Cl (the lysosomal pathway inhibitor) significantly attenuated the HG-induced reduction of Orai1 protein abundance. Moreover, HG treatment for 8 hours stimulated ubiquitination of Orai1 protein. We further found that HG treatment elevated the level of cellular hydrogen peroxide (H2O2) in a time-dependent manner. Treatment of cells with PEG-catalase significantly blunted the HG-induced reduction of Orai1 protein abundance. In addition, H2O2 itself also significantly decreased abundance of Orai1 protein and increased the level of ubiquitinated Orai1.

Conclusion: Taking together, these results suggest that HG treatment for a short-term, decreased the abundance of Orai1 protein in MCs by promoting its degradation through the ubiquitination-proteosome and –lysosome mechanisms. This HG-stimulated posttranslational regulation of Orai1 protein was mediated by H2O2.

Sponsor: NIH
IRB/IACUC#: N/A
Does the Relationship Between Activity Limitations and Mental Health Differ by Gender in Diabetic Adults Age 45 Years and Older?

Purpose: In the United States, there is a moderate prevalence of disability and mental illness among adults, with diabetes as a contributing risk factor. Given the limited research among diabetics, the purpose of this study was to determine whether the relationship between activity limitations and mental health differs by gender in diabetic adults age 45 and older.

Method: This cross-sectional analysis used data from the 2015 BRFSS for pre-diabetic and diabetic adults age 45 years and older from Arkansas, Tennessee, Oklahoma, and Alabama. Multiple logistic regression analysis was used to assess the relationship between mental health and activity limitations while controlling for depression, health conditions, weight status, age, ethnicity/race, marital status, education level, employment status, income level, and gender.

Results: About two-thirds of pre-diabetic and diabetic adults age 45 years and older reported less than 30 days of good mental health (33-36%) and less than half reported two or more activity limitations (36-42%). After controlling for socioeconomic, demographic, and health related variables, males with two or more activity limitations were about 3-5 times less likely to report good mental health in all four states. Likewise, females with two or more activity limitations were about 2-4 times less likely to report good mental health in all states except Arkansas. Additionally, depression was found to be significantly and inversely related to mental health in four of four states in both males and females.

Conclusion: Overall, mental health and activity limitations were found to be inversely related in pre-diabetic and diabetic adults age 45 and older. A major limitation of this study was the inability to assess the severity of disease states, and whether they were controlled with medication. General practitioners can expect to see a moderate prevalence of poor mental health and activity limitations in pre-diabetic and diabetic adults age 45 years and older, particularly in patients with a history of depression. Primary care providers should provide mental health screens and referrals in pre-diabetic and diabetic adult patients presenting with two or more activity limitations, especially in males. Additionally, providers should screen for activity limitations if pre-diabetic and diabetic adult patients present with poor mental health.

Sponsor: N/A
IRB/IACUC#: 2017-070
Losing the Protective Effect of Cognitive Aging in Mexican American Diabetics

Background: Diabetes is a serious health issue, affecting nearly 29 million people in the US. Mexican Americans (MA) have higher rates of diabetes, a risk factor for Alzheimer’s disease and mild cognitive impairment. Normal cognitive aging is associated with decline, not impairment, in some areas of cognition (processing speed, memory, etc). Diabetes may contribute to age associated cognitive decline and to the development of cognitive impairment. This study examines the effect of age on memory and executive functioning (EF) among diabetic and nondiabetic MA.

Methods: Data from 415 MA subjects from the Health and Aging Brain among Latino Elders study (HABLE) were analyzed. Participants were classified as diabetic (n=171) or non-diabetic (n=244) and young (50 to 64, n=326) or old (65 and older, n=89). All participants were classified as normal controls (i.e., no diagnosis of dementia or MCI). Each participant underwent an interview (i.e., medical history and medications), cognitive testing, blood tests, and medical examination, as well as informant interviews. Memory was assessed by the Ravens Auditory Verbal Learning Test (RAVLT) Recognition and Delayed Recall, while EF was measured by Trail Making Test (TMT) Parts A&B and CLOX Part 1&2. Analyses were split by diabetes status (diabetic, non-diabetic) and age group (young, old), using independent t-tests.


Conclusion: It was expected that younger participants would perform better than older participants on all cognitive tests, regardless of diabetic status. However, the results indicated that younger and older diabetics demonstrated a similar pattern of performance on measures of memory and executive functioning, suggesting that younger age may no longer be a protective for diabetics. This study was limited by small sample size and cross sectional nature of the data. Further research is needed to understand the impact of health risks on normal cognitive aging.

Sponsor: N/A

IRB/IACUC#: 2012-083
Safer Living with Diabetes: A Team Approach

Purpose

Few published reports have described the use of interprofessional diabetes education courses to improve clinical outcomes, including hypoglycemic events and hemoglobin A1c (HbA1c) in geriatric patients with Type 2 Diabetes Mellitus (T2DM). The complex nature of T2DM in older adults necessitates a team of healthcare providers to focus on the various aspects of the disease including pathophysiology, complications, medications, and diet. Additionally, because of the increased risk of falls and hospitalizations associated with hypoglycemia in older adults, this should be an essential component of any education course. The aim of our study is to determine the effect of interprofessional interventions in improving HbA1c outcomes and reducing hypoglycemic episodes in older adults with T2DM.

Methods

The ‘Safer Living with Diabetes’ diabetes education class is an interprofessional two-hour patient education course taught by a pharmacist, nurse practitioner, and dietician explaining the disease process, complications, medications, and healthy diet. Eligible patients were referred by their medical provider and must have been diagnosed with pre-diabetes or T2DM. Point-of-care HbA1c levels were collected in patients requiring clinical assessment. Prior to the course, the nurse practitioner and pharmacist met to review treatment plans for patients scheduled to attend the course. Following the course, attendees met with either the nurse practitioner or pharmacist to review their point-of-care HbA1c results for possible medication adjustments. Attendees then followed-up with either the nurse practitioner or pharmacist in the clinic as appropriate. Attendees were asked to complete a pre- and post-course questionnaire to assess diabetes knowledge.

Results

Thirty-five patients (28% female, 94% T2DM) participated in the diabetes education course from September 2016 to June 2017. Mean age of participants was 74 years. Pre and post course surveys found improvement in patient’s understanding of the risk of hypoglycemia. HbA1c levels were reduced following the education course (7.88% prior, 7.64% post). A follow-up telephone survey to determine number of hypoglycemic events and the participants’ overall thoughts of the course is planned.

Conclusion

An interprofessional diabetes education course appears to benefit HbA1c levels in older adults with T2DM.

Sponsor: N/A
IRB/IACUC#: 2017-049
Associations between dietary intakes of magnesium and calcium and overweight and obesity in US children from National Health and Nutrition Examination Survey (NHANES) 2003-2012

Magnesium and calcium are important micronutrients for normal growth and development, and they may play a role in the development of obesity. Previous studies showed abnormalities of serum magnesium and calcium levels were detected among obese children. We examine the associations between intakes of magnesium and calcium from food and overweight/obesity among children in a population-based cross-sectional study. A total number of 5,813 children aged 8 to 14 years from the National Health and Nutrition Examination Survey (NHANES) 2003 to 2012 were included in our analyses. Dietary intakes of calcium and magnesium were determined from 24-h dietary recalls. NHANES anthropometric measurements were used, and body mass index (BMI) and BMI-for-age percentiles were calculated for boys and girls. Based on the International Child BMI-cut-offs, overweight was defined as BMI ≥85% to BMI.

Sponsor: N/A
IRB/IACUC#: 2017-066

Purpose: Hemoglobin A1c levels are considered to be the best indicator of good glycemic control. Poor glycemic control leads to diabetic complications. The purpose of this study was to examine the relationship between diabetic complications and the frequency of hemoglobin A1c monitoring.

Methods: Behavioral risk factor surveillance system data from 2015 were analyzed to estimate the frequency of hemoglobin A1c monitoring in people with diabetes. Ordinal logistic regression was used to examine the association between frequency of hemoglobin A1c checks and diabetic complications.

Results: People with diabetic complications had higher proportional odds (adjusted odds ratio [AOR]=1.27; 95% confidence interval [CI] = [1.08, 1.50]) of checking hemoglobin A1c more frequently when compared to those without diabetic complications. For individual diabetic complications, those who reported having kidney disease (AOR = 1.23; 95% CI = [1.02, 1.50]), eye disease (AOR = 1.34; 95% CI = [1.12, 1.60]), and coronary heart disease (AOR =1.25; 95% CI = [1.03, 1.52]), showed statistically significant association with increased frequency of hemoglobin A1c checks.

Conclusion: Our results suggest that people with diabetes do not adhere to recommended care guidelines until complications develop. Interventions should focus on Hemoglobin A1c monitoring prior to complications developing to improve diabetic outcomes.

Sponsor: N/A
IRB/IACUC#: 2018-005
A Preliminary Look at the Effect of Light Exposure on Blood Glucose Levels of Overweight and Obese Teens

Purpose: Teens experience a puberty-driven delay in their circadian clock due to a mismatch in their internal and social clocks that increases their risk of adverse health outcomes. Disruption to the circadian system from ill-timed light exposure before bedtime and reduced melatonin levels produces adverse changes in glucose control and increases Type 2 Diabetes Mellitus (T2DM) risk. As such, teens may be more susceptible to developing T2DM. This study sought to provide better insight into the relationship between light exposure around the sleep period and risk of developing T2DM in this vulnerable and understudied population. We proposed that light levels would be positively associated with HbA1c levels in teens during the two hours before bedtime and during the sleep period.

Methods: Current analyses utilized baseline data from a 13-week pilot intervention study (PI: Roane) that examined the impact of a circadian-conscious intervention on T2DM risk. Teens and caregivers provided informed consent/assent. HbA1c levels (mmol/mol) were collected via finger prick. Teens followed a “typical” self-selected sleep schedule for 1-week while wearing a wrist actigraph (AMI MicroMotion Logger) to capture 24-hour sleep and light data. BMI %tile was calculated from in-lab measured height and weight. Mean lux, percent time above 20 lux, minimum lux, and maximum lux were calculated for the two hours pre-bedtime and during the sleep period. Correlation analyses were run to examine the association between light exposure and HbA1c due to small sample size.

Results: Teens (n=7) were age 16 years, 57% female, and 57% Hispanic with low to moderate T2DM risk. Mean BMI %tile was 97th, HbA1c was 5.4, and 57% exhibited Acanthosis Nigricans. Mean sleep period duration was 496 minutes (mean sleep duration during this period = 410 minutes). Correlation analyses were not significant; however, visual inspection showed sex-differences in HbA1c levels and different patterns in how light exposure during these two crucial periods may relate to HbA1c.

Conclusion: These pilot findings did not confirm an association between light exposure (lux) and HbA1c levels (mmol/mol) in obese and overweight teenagers. Findings were limited by a sample that was small in size and low in T2DM risk. Suggested sex differences in these data combined with documented sex differences in the literature support further examining sex differences in a larger sample with more diverse T2DM risk.

Sponsor: N/A
IRB/IACUC#: 2014-078
Management of Type Two Diabetes with Chronic Kidney Disease

Chronic kidney disease is a complex disease that occurs in over 200 million people worldwide. There are multiple causes, including: chronic hypertension, arteriolosclerosis and diabetes. Diabetic kidney disease occurs in about 40% of all patients with type two diabetes. Due to the insidious nature of renal damage and the high risk of both secondary hypertension and diabetic nephropathy caused by type two diabetes, early intervention and tight glycemic control are crucial to slowing the progression of renal disease. Renal disease in these patients also poses a complicated problem due to the fact that the effects and concentrations of typical drugs use to control type two diabetes, are partially dependent on renal function as are the unique side effects of each drug. Therefore, close monitoring and frequent adjustment of these medications is needed when managing a type two diabetic with chronic kidney disease. In this report, we offer a brief overview of management of patients with type two diabetes that also have chronic kidney disease and present the case of a 71 year old female with type two diabetes and recently diagnosed chronic kidney disease.

Sponsor: N/A
IRB/IACUC#: 2018-046
Effect of an evidenced-based diabetic ketoacidosis pathway in a pediatric emergency department on patient outcomes

Purpose: Our primary objective was to measure time to first insulin dose, before and after usage of a diabetic ketoacidosis (DKA) order set in a pediatric emergency department. We had multiple secondary objectives, including determining the relation of patient outcomes to time to first insulin (such as their length of stay in the ED, as well as inpatient admissions as a whole), and improving time to resolution of all DKA patients.

Methods: This project was implemented after an agreement between the Endocrine and Emergency Departments that the establishment of a guideline would be helpful; the ICFISH pathway was created and implemented. ICFISH is an acronym for identify, call endocrinology, fluids, insulin, status, and finally hand-off. The retrospective data collection occurred between October 1, 2014 and March 31, 2016. The prospective data collection was between November 1, 2016 and June 8, 2017. All patients admitted for DKA during this time frame were included, but patients with new-onset diabetes and transfer patients were excluded from analyses. Patient records were entered into REDCap and analyses were performed via SAS (Statistical Analysis Software). Time to resolution, length of stay, whether the patient was discharged from the ED, and whether patient was admitted to PICU were compared based on whether the patient was admitted before or after ICFISH implementation.

Results: A total of 198 patients met inclusion criteria, and 127 were excluded, leaving 71 patients. There was a statistically significant decrease in the time to resolution of patients on the floor or PICU from the pre-group to the post-group (p=0.032), as well as length of stay (p=0.004), ED discharge (p=0.028), and PICU admission (p=0.001).

Conclusion: A standardized order set to treat patients admitted for DKA, via the ICFISH pathway, leads to decreased variability, thus resulting in shorter length of stay in the hospital overall, decreased PICU admissions, and increased ED discharge.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Application of an Interprofessional Student Exercise to Improve Nutritional Wellness in a Pediatric Clinic

Purpose: Childhood obesity has become a significant problem in the state of Texas, especially in Tarrant County. To address the substantial nutritional education deficiency in the outpatient setting, faculty members of the UNTHSC pediatric clinic initiated a collaboration with the Interprofessional Education (IPE) department at UNTHSC. In collaboration with the dietetic departments at Texas Christian University and Texas Woman’s University, an outpatient internship was established for dietetic students at the UNTHSC pediatric clinic. A qualitative assessment was constructed to establish the success of the interns in the clinical environment and whether dietary information was delivered effectively to the patient and family.

Methods: After the multi-faceted interprofessional team including a pediatrician, dietetic intern and medical/PA student concluded the visit with the patient, the patient’s parent received a short anonymous survey completed in the clinic. 4 questions assessed the quality and satisfaction of the visit using a 5-point Likert scale. Only families who had been consulted by the interprofessional team received the survey.

Results: One hundred and twenty-one respondents filled out the survey, with 101 being parent/guardians, 17 patients 18+ years of age, and 3 other family members. 86% believed the addition of a dietitian improved the quality of the visit, and 90% were satisfied with the visit as a whole. The addition of the dietary information was viewed as very helpful with 87.6% of parents or patients pledging to apply this information in the near future.

Conclusions: The addition of a dietary intern to supplement the dietary education during pediatric visits was well received by patients and parents. By incorporating an Interprofessional team in the patient care, patients can have more of their needs and concerns addressed by a specialist in that field. By working with other institutions, this model of Interprofessional care can be successfully utilized within other local clinics and further applied with other medical professional schools.

Sponsor: N/A
IRB/IACUC#: #2017-119
Medical Students' Practice of EPAs in Service Learning

Purpose

Community service learning activities meet a wide range of learning objectives: exercising clinical skills which includes taking vitals, histories and physicals, preventive health screenings and health education, injury prevention and first aid, collaborating with other members of the health care team as well as providing care under supervision for the most underserved and vulnerable populations, and addressing population health.

Many of the direct service experiences enable students to work with patient records, dispense donated medicines, practice forming clinical questions, collecting patient data and interacting directly with real patients practicing interviewing skills, patient centered care and empathy. Many of the health education and safety service experiences enable students to recognize factors affecting population health and opportunities to develop strategies to improve the overall health of our communities.

Methods

Self-report data from osteopathic medical students’ required service is required for each activity or event and since Fall 2015 is collected electronically. Data includes the type of service, and Likert scale ratings of students overall satisfaction with the experience, and the extent to which each activity meets certain learning objectives. Specific service activities exercise specific EPAs, and students ratings can indicate whether the learning objectives for those EPAs have been met.

Results

Data from 920 students with a total of 7,490 service evaluation reports are available for analysis. The most common types of service are assisting at indigent clinics, health fairs, sporting events, health education and safety for children and direct health services including OMM. The majority of students strongly agreed or agreed the overall experience of a specific event was good for of them. The majority strongly agreed clinical skills, health education and collaboration learning objectives were met during homeless services events and for mission trips.

Conclusions

Service learning is designed to provide opportunities for students to engage in experiential learning which is task and problem specific, improves clinical skills, and experience the benefits of altruistic behavior. The model of learning applied here originated with John Dewey (1938) and developed by Kolb (1984), and Boyatzis (2000) to address professional competencies. This is a step in understanding on the impact of service learning in meeting specific learning objectives in medical education.

Sponsor: N/A
IRB/IACUC#: IRB # 2015-159
Service Learning: Doctor of Physical Therapy Year 1 Student Reflections After Participating in a Runner’s Health and Fitness Expo.

Purpose: This study further investigated the role a short-term service learning activity at a runner’s health and wellness expo had on Doctor of Physical Therapy (DPT) students. We hypothesized that after participating in this SL experience, DPT students will report improved ability to interact with clients, enhanced understanding of previously learned curricular content, and the expectation of improved clinical rotation experiences.

Methods: First-year DPT students performed Functional Movement Screens (FMS) on community participants during 3-4 hour shifts at a runner’s health and wellness expo. Forty-seven first-year DPT students, 30 females and 17 males, mean age of 25 years (22-32). Outcomes were assessed using a post-survey completed by the students through Qualtrics.

Results: The majority of student responses indicated a positive impression of this SL. Means of responses to detailed questions were high (4.21-4.66) covering student perceptions of the role of SL in the DPT curriculum, the impact of SL on clinical education, and the usefulness of this particular SL experience for future classes. Forty-seven percent (22 of 47) reported being no more than somewhat familiar with SL prior to participating. Following this activity, 91% (43 of 47) agreed that this SL experience furthered their understanding of curricular content, 96% (45 of 47) valued the importance of physical therapist participation in SL activities, and 96% (45 of 47) agreed that this SL opportunity should be kept in the curriculum for future cohorts.

Conclusions: The findings from this study were consistent with the hypotheses that students would report improved ability to interact with clients, enhanced understanding of previously learned curricular content, and the expectation of improved clinical experiences. This sample was limited to one cohort of year 1 DPT students at UNTHSC in Fort Worth, TX. Data may not be generalizable beyond these conditions. This SL experience gave students the opportunity to interact with community members and apply classroom knowledge at a health and fitness expo. This type of interaction allows students to practice using patient-friendly instructions and explanations which will be beneficial during clinical rotations and novice clinical practice.

Sponsor: N/A
IRB/IACUC#: 2013-190
Managing Safety and Efficacy In ADHD: A New Wave Of Approaching Treatment Options

 PURPOSE: Attention Deficit and Hyperactivity Disorder (ADHD) is a common neurologic disorder affecting approximately 9% of the population according to the National Center for Health Statistics. A variety of diagnostic and treatment guidelines exist, complicating the pharmacological and nonpharmacological treatment options. The objective of the study was to summarize key aspects in the diagnosis and treatment options in children with ADHD through a systematic review of current literature.

 METHODS: The following databases were searched: MEDLINE, PubMed, and Scopus for meta-analysis, randomized control trials, and other systematic reviews in English, children or adolescent study group, and published between 2007 - 2017. Two authors independently assessed the results of each database and disagreements were resolved through discussion. An algorithm was developed and EBM grading scales were utilized to evaluate quality. Five main topics were evaluated based on a preliminary relevancy search. Topics included: ADHD diagnosis, pharmacologic treatment options and safety profile, and efficacy of non-pharmacologic options including diet and cognitive behavioral therapy. Search terms included ADHD, stimulant, safety, diet, and cognitive behavioral therapy. Selection criteria for relevant studies included those with a control group, randomization, used an official ADHD rating scale to determine efficacy, and ADHD as a primary diagnosis.

 RESULTS: A variety of guidelines exist regarding ADHD diagnosis. Most follow DSM-IV (or updated DSM-V) although no clear consensus has been developed. However, based on a patient’s age, stimulants are a typical first line therapy in treating children and adolescents with ADHD. Stimulants pose a variety of safety concerns including reduced appetite, insomnia, and cardiovascular events. Based on stigma regarding stimulant use, parents have sought nonpharmacologic options to therapy. The primary nonpharmacologic option is behavioral therapy (as an adjunct to medication or alone). Dietary changes and supplementation have shown potential additional benefits.

 CONCLUSION: ADHD remains a prevalent and growing topic among parents, teachers, caregivers, and healthcare providers. Individualization plays a key role in determining treatment. Depending on the patient’s current health status, medical history, and use of other medications, parents need to work with their physician and pharmacist to determine the best treatment.

 Sponsor: N/A
 IRB/IACUC#: N/A
Orthopedic Implants With Imaging Correlation

Purpose:

Orthopedic surgery is an important discipline that encompasses numerous procedures that entail placement of various pins, screws, plates, rods, prostheses, and other hardware. Virtually every healthcare provider will encounter many patients with orthopedic implants; however, medical students at the Texas College of Osteopathic Medicine have minimal hands-on exposure to such implants. Presented here are 16 orthopedic implants matched with corresponding radiographic images. This exhibit allows students to personally handle different pieces of hardware while visualizing how and where they are used in orthopedic procedures.

Methods:

The surplus orthopedic hardware on display was donated to our team by the Baylor Surgical Hospital at Fort Worth. We then identified each implant and searched the internet for matching radiographic images that demonstrate their in vivo utilization in actual patients.

Results and Conclusion:

We successfully identified 16 orthopedic implants and obtained correlative radiographs. This Poster, which will remain accessible to students on permanent display in a school laboratory, is a unique educational tool which allows students to directly interact with real orthopedic implants while comprehending their utility through via correlative imaging.

Sponsor: N/A
IRB/IACUC#: N/A
Implementation of a Peer Writing Accountability Group to Improve Scholarly Productivity: A Quest for Protected Time

Purpose: The pursuit of scholarly activity is a well-described expectation of health sciences faculty given their role in the advancement of public health and patient wellness. Full-time faculty—who maintain clinical teaching sites and service responsibilities—have unique challenges when asked to focus on research. Recommendations for successful scholarly endeavors include formal mentoring, participation in clinical research programs, collaboration with faculty with proven research experience, and involvement in writing groups. A peer-to-peer writing accountability group (WAG) was established at the UNT System College of Pharmacy in June 2017. The objective of this study was to evaluate the impact of the WAG on scholarly productivity among health sciences faculty.

Methods: This study was approved by the UNTHSC IRB in June 2017. The WAG consisted of a small number of pharmacy faculty who met weekly from June 2017-August 2017 to work on scholarly activity. Pre- and post-surveys were administered to all participants. Descriptive analyses were performed to assess writing session duration and quantity of scholarly activity. A paired t test was used to determine differences before and after WAG participation. For all statistical tests, alpha level of significance was set at 0.05. Qualitative data based on responses to open ended questions was content analyzed to identify themes.

Results: Ten (100%) faculty involved in the WAG completed pre- and post-surveys. Average writing session duration was 2.1 to 2.9 hours, while number of pages written, abstracts submitted, and presentations provided was 17-24, 1-2, and 1, respectively. Mean scores for the pre- and post-test were: average number of publications accepted (2, 1); writing frequency where 0=Daily and 3=Rarely (2.4, 1.6); current time management is sufficient (3, 1.7), current organization skills are sufficient (2.3, 1.5) where 0=Strongly Agree and 4=Strongly Disagree (p)

Conclusion: Participation in a peer-to-peer WAG increased productivity, time management, and organization skills with regards to scholarship. WAG could be an effective tool to improve scholarly productivity among health sciences faculty.

Sponsor: N/A
IRB/IACUC#: 2017-071
Bi-functional small molecule with both IOP lowering and neuroprotective activity to treat glaucoma.

Purpose: The multifaceted pathology associated with glaucoma is difficult to treat by monotherapy such as lowering intraocular pressure (IOP). Oxidative stress is involved in IOP elevation and retinal ganglion cell (RGC) death possibly via decreased activity of antioxidant enzymes. Our hypothesis is that, a small hybrid molecule SA-2 and its PLGA encapsulated nanoparticle (NP) drug delivery vehicle (SA-2-NPs) possessing a nitric oxide (NO) donating group and a redox antioxidant moiety will lower IOP as well as possess neuro/cytoprotective potential.

Methods: IOP-independent neuroprotection of RGCs: Mice (C57BL6, 12 weeks, n=8) were anesthetized and the optic nerve crush (ONC) was performed on one eye followed by intravitreal injection of 2ml of 2% SA-2 formulated in PBS or vehicle to the crushed eye at day 0 and 3. At day 7, pattern electroretinogram (PERG) was performed, following which retinas were flat mounted. Number of surviving, RBPMS positive RGCs were counted. IOP lowering effect: Nine Brown Norway normotensive rats (n=3 per each group) were used to evaluate the IOP-lowering properties of SA-2-NPs under a masked protocol. Topical eye drops (30 µL/drop) containing: A) Vehicle (PBS), B) Travoprost (0.004%)-positive control or C) SA-2-NPs (100 µg/mL) formulated in PBS were administered in three rats and IOP was measured using the TonoLab rebound tonometer at various time points: 0, 3, 6, 24, 48 and 72 h post-dosing. The entire dosing schedule was repeated 3 times in each rat.

Results: Compound SA-2 treatment was significantly (t-test, p < 0.001) effective in protecting RGC against ONC induced death. Density of RGCs for PBS treated mice was 1000 cells/cm² vs SA-2 treated group (2100 cells/cm²) and was comparable to the untreated control (2650 cells/cm²). The data are given as the mean ± SEM; n= 3-4. PLGA encapsulated SA-2-NPs (100mg) statistically (t-test, p < 0.001) lowered the IOP in treated eyes by 19% and 21% at 24 and 48h respectively in comparison to contralateral control eyes. Travoprost was statistically effective in lowering IOP in treated rat eye by 14% at 6h.

Conclusion: Taken together, our results are consistent with our hypothesis that this novel class of hybrid compound and its PLGA encapsulated nanoparticles will decrease IOP and protect RGCs from cell death. Further structure optimization of the lead compound, dose optimization, IOP lowering study in ocular hypertensive rodent models are underway.

Sponsor: N/A
IRB/IACUC#: IACUC-2016-0030
Discovery of new agents to inhibit scarring and improve the success of glaucoma surgery

Purpose:

Glaucoma is a common ophthalmological condition related to elevated intraocular pressure (IOP). Glaucoma can sometimes be treated surgically with a procedure called a trabeculectomy that allows for increased drainage of the aqueous humor of the eye to reduce the IOP. After this surgery, many patients develop a scar at the surgical site that can reverse the benefits of the surgery. This study aims to compare multiple inhibitors of the TGFβ2-TLR4 signaling pathway against the current standard treatment for scar inhibition to determine if they could be more effective. Less scarring would lead to better maintenance of lower IOP and more successful glaucoma surgeries.

Methods:

Primary human conjunctiva/tenon fibroblast cell strains were treated with Mitomycin C (MMC), the standard treatment to prevent scarring, TAK-242 (a selective inhibitor of TLR4), or NBP2-29328 (a selective inhibitor of MyD88). NBP2-29328, TAK-242, and untreated cells were incubated with 0.5% FBS for 24 hours, and MMC cells were incubated for 5 minutes. Next, a wound scratch assay was performed. Each well was photographed with a Keyence imager at 0, 6, 24, 48, 72, and 96 hours post-scratch. Using ImageJ software, the 0-hour images were analyzed to get an area value and a ROI (Region of Interest) outline of the 0-hour scratch. The later images were analyzed to get values for the number of cells present and their total area covered. The four treatments were compared for efficacy of inhibition of cell migration and proliferation. This protocol has been performed in two studies.

Results:

There were significant differences between treatments at 72 and 96 hours. In the first study, inhibition from the MMC treatment was significant compared to control (p

Conclusions:

The data from the studies suggest that these treatments may be useful for scar inhibition after glaucoma trabeculectomy surgery.

Sponsor: The Cure Glaucoma Foundation

IRB/IACUC#: N/A
Inhibition of chronic endoplasmic reticulum stress rescues myocilin-associated glaucoma via stimulation of autophagic flux in the TM

Purpose: We have previously demonstrated that expression of mutant myocilin leads to chronic ER-stress induced transcriptional factors such as ATF4 and CHOP, which may lead to TM dysfunction and IOP elevation. Here, we explored whether and how genetic knockdown of ATF4 or CHOP rescues myocilin-associated glaucoma.

Methods: Autophagic flux was monitored in Tg-MYOCY437H mice and primary human TM cells using adenoviral expression of RFP-GFP-LC3 and analysis of key autophagy markers LC3B and P62. Key mediators of chronic ER stress, ATF4 or CHOP were knocked down using CRISPR-Cas9. Myocilin accumulation and autophagic flux was examined in TM cells and Tg-MYOCY437H mice. We further examined whether stimulation of autophagy via Tat-Beclin 1 peptide or Torin 2 on glaucoma phenotype and mutant myocilin accumulation using mice and TM cells.

Results: Expression of mutant myocilin impaired autophagic flux in primary TM cells and in the TM of Tg-MYOC Y437H mice as evident from increased LC3BI/II ratio, p62 and decreased red/yellow puncta of RFP-GFP-LC3B constructs. CRISPR-Cas9 mediated ATF4 or CHOP knockdown in TM cells stably expressing mutant myocilin improved autophagic mediated degradation of mutant myocilin, as evident by an increased LC3II/LC3I ratio, decreased P62, decreased mutant myocilin accumulation. Increased colocalization of LC3 with mutant myocilin in lysosomes was observed in ATF4 or CHOP deleted TM cells demonstrating active autophagic degradation of mutant myocilin. A dose dependent decrease in mutant myocilin accumulation was observed upon Tat-Beclin 1 treatment of TM cells expressing mutant myocilin. Tat-Beclin 1 or Torin 2 (autophagy inducers) treatment reduced intraocular pressure in Tg-MYOCY437H mice. Moreover, Western blot analysis of mice anterior segment lysates demonstrated induction of autophagy markers and reduction of mutant myocilin accumulation.

Conclusions: Genetic knockdown of ATF4 or CHOP increased autophagy flux, and facilitated autophagy-mediated clearance of accumulated mutant myocilin. Moreover, chemical induction of autophagy reduced mutant myocilin and rescued glaucoma in mice further suggesting the feasibility of targeting autophagy for the treatment of glaucoma.

Sponsor: EY026177
IRB/IACUC#: 2015/0002
Using Grapes as a Magic Bullet to Fight Against Free Radicals in the Eye: Application for Cataract Prevention

Purpose: The main purpose of this study is to investigate if grape powder could protect against in vivo ultraviolet (UV) radiation-induced cataract and to study its mechanism of action and identify its targets in the lens.

Methods: The grape powder was provided by the California Table Grape Commission (CTGC). C57BL/6J mice were feed with the regular diet, regular diet supplemented with glucose and fructose, or the grape diet (regular diet supplemented with 5%, 10%, and 15% grape powder) for 3 months. The animals were then exposed to 20.6 kJ/m² UV radiation for 15 min to induce cataracts. Two days later, the degree of the cataract and lens morphology was evaluated under dissecting microscope. Glutathione (GSH), free protein thiol (PSH), and protein glutathionylation (PSSG) levels were measured to reflect the oxidative markers. Finally, we also examined the effects of grape powder on the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway and its downstream antioxidant genes in the lens.

Results: We found that 15% grape powder diet could significantly inhibit the onset as well as the severity of UV-induced cataracts. All mice in the regular diet control group developed severe epithelial and superficial anterior subcapsular cataracts two days after the UV radiation. On the other hand, grape powder diet in a dose-dependent manner prevented the lens from UV radiation-induced cataract progression. In the 15% grape powder diet group, the majority of lenses remained largely transparent. The GSH and PSH levels were much higher in the 15% grape powder diet group compared with that of the regular diet control group. The accumulation of PSSG, a marker for protein thiol oxidation, was largely inhibited in the 15% grape powder diet group. Interestingly, we also found that Nrf2 and its downstream targets including SOD, catalase, thioredoxin (Trx), and glutaredoxin 1 (Grx1) were significantly elevated in regular diet control groups due to the UV exposure. However, this UV-induced Nrf2 activation was largely inhibited in all three grape powder diet groups.

Conclusions: Grape powder dose-dependently protected the lens from UV radiation-induced cataract development in mice. Its protective effects may involve directly regulating endogenous Nrf2 and its downstream target detoxifying/antioxidant genes, including SOD2, Catalase, Trx1 and Grx1.

Sponsor: California Table Grape Commission Grant RP20011; Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R25HL125447 (to Dr. J.K.Vishwanatha).

IRB/IACUC#: 2016-0010
Glucocorticoid-induced ocular hypertension leads to progressive retinal ganglion cell loss, impaired axonal transport and optic nerve degeneration in mice

Purpose: Ocular hypertension (OHT) and secondary iatrogenic open angle glaucoma are the serious side effects of glucocorticoid (GC) therapy, which is used widely to treat various immune mediated diseases. We have previously developed a novel mouse model of GC-induced OHT using weekly periocular injections of potent GC, dexamethasone (Dex). The purpose of this study is to examine whether sustained Dex-induced OHT leads to glaucoma phenotype in mice.

Methods: Three-month old C57BL/6J mice (n=30) were injected with either Dex-Acetate (200µg/eye) or vehicle suspension via periocular route, once in a week for 10-weeks. IOP was measured every week and pattern electro retinogram (pERG) was used to measure RGC function at 10-weeks post injections. Alexa Flour 594-cholera toxin B (CTB) was injected intravitreally, to trace the deficits in anterograde axon transport. Abnormal extracellular matrix (ECM) deposition in trabecular meshwork (TM) was assessed by immunostaining. RGC loss was analyzed by whole mount retina staining with RBPMS antibody and axon degeneration was examined by PPD staining.

Results: Weekly injections of Dex but not vehicle caused sustained and pronounced IOP elevation in mice, starting from 1-week of injection (Δ ≥3.5mmHg IOP). In addition, Dex reduced the outflow facility (~30%) and also induced abnormal ECM proteins (fibronectin and collagen I) deposition in TM. pERG revealed significant deficits in RGCs function as evident from reduced pERG amplitudes (10µV v/s 25 µV) with increased N1 latency periods (140ms v/s 100ms) in Dex-injected mice compared to vehicle injected mice. Importantly, we observed a highly significant RGC loss in Dex-mice (loss was ~60% in periphery and ~50% in mid-periphery). Axon anterograde transport tracer CTB accumulated in ONH of Dex-mice, indicating deficits in axonal transport. PPD-stained cross sections of optic nerves showed severe axonal damage in Dex-mice, whereas no damage was observed in vehicle injected mice.

Conclusions: These data suggest that our novel mouse model of periocular Dex-induced OHT develops glaucoma phenotype. Also, there are many clinical, morphological, and molecular similarities between our Dex-induced glaucoma model and POAG, making this mice model as an attractive model to study the specific aspects of POAG, including TM and RGCs pathology in glaucoma.

Sponsor: 5R00EY022077-04
IRB/IACUC#: 2015/0002
Are Smokers More Likely to be Non-Compliant with their Medications? An Examination of Permanent Supportive Housing (PSH) Residents in Fort Worth, Texas

Purpose: People with a history of chronic homelessness are disproportionately more likely to smoke and have problems with medication compliance. Moreover, smoking and medication adherence are often related; people who smoke tend to have more trouble taking their medications. However, no studies to our knowledge have investigated this relationship among a group of formerly homeless individuals who have mental health symptoms. The current study utilized a sample of permanent supportive housing (PSH) residents in Ft. Worth, TX who were participating in a health coaching program. It was hypothesized that people who smoked would have more difficulties adhering to their medication regimens.

Methods: Data were from m.chat, a technology-enhanced health coaching program for PSH residents with mental health symptoms. Data from November 2014 - March 2017, which consisted of 567 participants, were included. Baseline smoking status was determined by the following question: do you currently smoke cigarettes, or use other forms of tobacco? (yes vs. no). Medication adherence was identified using a modified Morisky Medication Adherence Scale, which categorized people as low vs. medium/high adherence. Covariates were selected based on prior literature and the information available in our data. Logistic regression was used for the analysis.

Results: Medication adherence was similar between smokers and non-smokers (aOR: 0.78, 95% CI: 0.41, 1.49). However, drug abuse was significantly associated with medication adherence; people who reported consuming any illicit drug or abusing a prescription medication in the past 90 days had 73% lower odds (aOR: 0.27, 95% CI: 0.12, 0.65) of adhering to medications compared to those who reported no drug abuse. Alcohol consumption was significant in the unadjusted analysis, but was not significant after adjusting for other factors.

Conclusions: Among a group of PSH residents with a history of homelessness, smokers and non-smokers had similar rates of medication adherence. Although smoking was not associated with medication adherence, other forms of substance use were related to a poorer medication adherence. This research highlights the role of illicit drug use in predicting medication adherence; programs that attempt to improve rates of medication adherence should take drug use into account as a key predictor of compliance.

Sponsor: N/A
IRB/IACUC#: 2014-125
TRPV4-mediated regulation of intraocular pressure and outflow facility in mouse model of glucocorticoid-induced ocular hypertension

Purpose: Increased intraocular pressure (IOP) due to increased outflow resistance to aqueous humor at the trabecular meshwork (TM) is one of the major risk factor associated with glaucoma. Transient receptor potential channel vanilloid isoform 4 (TRPV4), a polymodal cation-permeable channel, has been implicated in mechanotransduction. Increased IOP and reduced outflow of aqueous humor may compromise the mechanosensory signaling in the trabecular meshwork. We hypothesize a dysfunction in the mechanotransduction pathway in the TM of hypertensive eyes, and propose a physiological role for TRPV4 channels in regulation of IOP and outflow facility.

Methods: The effects of TRPV4 activation was studied using recently developed mouse model of glucocorticoid-induced ocular hypertension. 20 mL of 10 mg/mL dexamethasone-21-acetate (Dex-Ac) formulation was administered weekly to both eyes of C57BL/6J mice via periocular conjunctival fornix injections. Ocular hypertensive mice were topically administered 1 mM GSK1016790A (TRPV4 agonist) in one eye and DMSO vehicle in the contralateral eye. The subsequent effect on IOP was recorded 15, 30, and 60 min intervals after the eye drops and weekly in isoflurane anesthetized mice. Outflow facility was further examined in ocular hypertensive mice treated with 1 mM GSK1016790A eye drops 1 hour prior to the measurements.

Results: Weekly periocular injections of Dex-Ac showed significant increase in IOP greater than 5 mmHg, when compared to vehicle control \( (P<0.001) \). In ocular hypertensive mice, topical administration of TRPV4 activator caused significant and sustained decrease in IOP back to baseline levels, when compared to vehicle treated contralateral eyes \( (P<0.001) \). IOP measurement at different time points following TRPV4 activation showed a rapid effect on IOP within 60 minutes \( (P<0.05) \). Measurement of outflow facility via the constant-flow infusion method shows a significant increase in outflow facility one hour after topical administration of TRPV4 agonist when compared to the vehicle treated contralateral eyes \( (P=0.026) \).

Conclusion: Our data provides physiological evidence for the positive effect of TRPV4 activation on IOP and outflow facility. Further work is required to elucidate the underlying molecular mechanisms behind TRPV4-mediated effect on IOP and outflow facility.

Sponsor: NEI Grant R01EY026177
IRB/IACUC#: 2015-0002
Transcorneal Permeability Pilot Studies

Purpose: Permeability of potential ocular agents across the cornea is important in evaluating their ability to enter the eye by the transcorneal route. Accordingly, the purpose of this study was to set up a transcorneal permeability protocol and develop the necessary analytical methods to evaluate flux differences among test agents across cornea from different species.

Methods: Corneas from rat, pig and rabbit were used. Jacketed vertical diffusion cells were used to test transcorneal permeability. Two test compounds of comparable molecular volume but differing in lipophilicity (measured by the logarithm of the n-octanol/water partition coefficient, logP) by approximately two log units were chosen for this pilot study. Once cornea and cell chambers were equilibrated to 35°C, cornea was mounted and test compounds at a given concentration either in saline or in saline containing a permeability enhancer excipient were placed in the donor chamber. The amount of test agents in the receiver chamber versus time was measured based on methods developed in our laboratory and using LC-MS/MS selected reaction monitoring on a TSQ Quantum Ultra (Thermo) connected to a Surveyor HPLC system (Thermo). Quantification of each test compound was performed based on the principles of stable isotope dilution. Flux was calculated, based on the principles of diffusion testing.

Results: We were able to establish the transcorneal permeability procedure for testing the diffusion of compounds across the cornea. In addition, selected reaction monitoring LC-MS/MS quantification methods were developed for the test compounds. Of our two test compounds in this pilot study, we were able to show that the flux across the cornea for test compound with intermediate lipophilicity was approximately one log unit higher for all species when saline vehicle was used and about 0.5 log unit higher when a permeability enhancer excipient was used, compared to those of test agent with high lipophilicity (logP about 4).

Conclusions: This pilot study showed the establishment of a protocol for a convenient evaluation of the transcorneal permeability of test compounds quantified by LC-MS/MS analyses.

Sponsor: This study was supported by NIH grant R01EY027005 (KPT)
IRB/IACUC#: 2014/15-39-A08
Crosstalk Between TGFβ2 and TLR4 in the Trabecular Meshwork

Purpose: The trabecular meshwork (TM) regulates aqueous humor outflow and intraocular pressure (IOP). The effects of TGFβ signaling pathways on the TM extracellular matrix (ECM) have been extensively studied. Recently, we identified TGFβ2 and toll-like receptor 4 (TLR4) signaling crosstalk regulates changes in the TM ECM and mutation in Tlr4 rescues TGFβ2-induced ocular hypertension in mice. Here, we investigated the role of an endogenous TLR4 ligand, FN-EDA, and a downstream signaling molecule of TLR4, NFκB, in TGFβ2-induced ocular hypertension in mice.

Methods: B6.FN-EDA−/− (n=18), B6.FN-EDA+/+/TLR4−/− (n=7), B6.FN-EDA−/−/TLR4−/− (n=15), and C57BL/6J (n=11) mice were intravitreally injected with 2.0 μL Ad5.TGFβ2 (2.5x10^7 pfu) in one eye and the contralateral uninjected eye was used as a negative control. Likewise, we tested mice lacking the p50 subunit of NFκB (B6.Cg-NFκB1tm1Bal/J) (n=7) and C57BL/6J (n=10) mice. IOP was measured using a TonoLab rebound tonometer on isoflurane-anesthetized mice for 42 days post-injection. Significance determined by one-way ANOVA at each time point.

Results: Ad5.TGFβ2 significantly induced ocular hypertension in C57BL/6J mice in both experiments. In the first experimental cohort, Ad5.TGFβ2 significantly induced ocular hypertension in C57BL/6J mice starting at 7-days post injection and remained significant until 42 days post-injection (p

Conclusions: These findings demonstrate that TLR4, the endogenous TLR4 ligand FN-EDA, and NFκB are necessary for TGFβ2 induced ocular hypertension in mice. These data provide potential new targets to lower IOP and to further explore the molecular mechanisms involved in the development of glaucomatous TM damage.

Sponsor: NIH Grant 1R01EY026529, NIH Grant 3R01EY026529-02S1
IRB/IACUC#: IACUC-2015-0002
A Mechanism study toward understanding the protective effects of glutaredoxin 2 (Grx2) on light-induced retinal damage

Purpose: Glutaredoxin 2 (Grx2), located mainly in the mitochondria, is a glutathione-dependent oxidoreductase which is known to reduce S-glutathionylated proteins. In previous study, we have found that Grx2 could protect the retina from light-induced retinal degeneration. However, the molecular mechanisms that coordinate mitochondrial energy production with thiol-repair processes in the damaged retina remain largely unknown. To better understand the protective effects of Grx2 in the retina, our study was thus extended to analyze the full transcriptome changes of the retinal tissue in light-exposed Grx2 knockout (KO) mice.

Methods: Wild type (WT) and Grx2 KO mice were exposed to white light at 12,000 lux for 1 hour after dark adaptation. The retinal damage was confirmed by the electroretinogram (ERG) recording and spectral domain optical coherence tomography (SD-OCT) measurement. Protein glutathionylation level was evaluated by Western Blot. We then compared the full transcriptome of the retinal tissue in WT and Grx2 KO mice by performed the whole transcriptome shotgun sequencing (RNA-seq). The gene network was analyzed using DESeq2 pathway analysis software and the selected genes of interest were further confirmed by real-time PCR and Western Blot.

Results: Light-exposed Grx2KO mice showed compromised visual function as indicated by severe loss of both a- and b-wave amplitudes and the thinning of the outer nuclear layer (ONL). Protein glutathionylation level was elevated in light-exposed Grx2 KO mice. We identified thousands of genes with statistical significant expression changes in light-exposed Grx2KO mice and classified them into cellular processes and molecular pathways. Among these pathways, many genes that are related to complement activation and inflammation reaction were significantly upregulated. These genes include complement C3, C4a, C4B (C4B), Bcl-3, NF-kappa B, Jak3, and STAT3.

Conclusions: Collectively, our results suggest that Grx2 could protect the retina from light-induced retinal degeneration. It plays an important role in regulating light-induced retinal inflammation which may be associated with its ability to reduce S-glutathionylated substrates.

Sponsor: 1.BrightFocus Foundation Project(RP0239) 2.Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R25HL125447 (to Dr.J.K.Vishwanatha).

IRB/IACUC#: 2016-0010
Does Physical Activity Level Differ Between Those With and Without Diagnosed Arthritis in Middle Aged Females?

Purpose: Current clinical guidelines regarding the recommended physical activity levels for middle aged females with arthritis are unclear. Therefore, the purpose of this study was to assess whether physical activity levels differ between those with and without diagnosed arthritis in middle-aged females.

Methods: This cross-sectional analysis used 2015 BRFSS data for females ages 45-64 from Arkansas, Mississippi, and Alabama. Multiple logistic regression was used to assess the relationship between physical activity levels and arthritis while controlling for weight status, fruit consumption, vegetable consumption, activity limitations, heart disease, depression, educational level, and ethnicity/race.

Results: Approximately half of females 45-65 years-old reported a diagnosis of arthritis (44-49%) and less than half reported being physically inactive (38-45%). Overall, physical activity levels did not significantly differ between those with and without arthritis. However, arthritis was significantly related to activity limitations, heart disease, and depression.

Conclusion: Overall, physical activity levels did not differ between those with and without arthritis in females ages 45-64 years old. Across 2 or 3 states, an arthritis diagnosis was significantly related to activity limitations, a diagnosis of angina or coronary heart disease, and a diagnosis of depression. However, no information was available regarding patient medications, compliance, or current management of arthritis. Based on the results of this study, it is recommended that if a patient presents with arthritis, activity limitations, coronary heart disease, or depression, primary care providers should screen for all four conditions, provide education, and treat accordingly.

Sponsor: N/A

IRB/IACUC#: 2017-070
A Case of Valentino’s Syndrome Presenting as Possible Appendicitis

Background: One of the most common causes of right lower quadrant abdominal pain is acute appendicitis. The most frequent symptoms observed are periumbilical pain that radiates to the right lower quadrant, anorexia, nausea and vomiting. Other conditions which mimic acute appendicitis at presentation include ovarian torsion, ruptured ectopic pregnancy, pseudomembranous colitis, and perforated cholecystitis. Here, we present a unique case of Valentino’s syndrome, wherein a perforated duodenal ulcer manifested the same constellation of symptoms as acute appendicitis.

Case Information: When computed tomography and ultrasound were not definitive for the diagnosis, the decision was made to perform a laparoscopic appendectomy. The appendix showed no gross signs of inflammation, so intraoperative esophagogastroduodenoscopy was used to examine for a perforated peptic ulcer. When no perforations were found, exploratory laparotomy was performed and revealed purulent fluid in the right colic gutter and a pinhole perforation in the first part of the duodenum. The defect was repaired and the abdominal space was washed thoroughly and closed. The patient recovered well and was discharged from the hospital in good health.

Conclusion: Valentino’s syndrome is an uncommon cause of RLQ pain and symptoms mimicking acute appendicitis.

Sponsor: N/A
IRB/IACUC#: 2018-074
Would Guidelines for Maturity Onset Diabetes in Youth (MODY) Be Useful in Clinical Practice?

Purpose: Maturity Onset Diabetes in Youth (MODY) is a rare form of diabetes mellitus (DM) caused by a single gene mutation inherited in an autosomal dominant fashion. There are approximately 13 different gene mutations that can cause the MODY phenotype. MODY is typically diagnosed in Caucasian adolescents; the incidence is similar in males and females. Approximately 80-95% of MODY cases are misdiagnosed as T1D or T2D. Currently no algorithm is available to facilitate clinic decision making to assure proper diagnosis and treatment of affected youth.

Methods: An online survey was conducted to better understand common approaches in the diagnosis of DM in youth and the need for a clinical algorithm to help guide testing for MODY. The survey was sent via email to PESTOLA providers (Pediatric Endocrinologists of Texas, Oklahoma, Louisiana, and Arkansas).

Results: The survey was sent out to 188 providers; 32 responded (17% response rate). In establishing a diagnosis of MODY, a majority of providers agreed or strongly agreed that they needed more education (53%) and that they needed and algorithm (64%). Responses to the survey allowed us to construct a cost-effective diagnostic algorithm to assist in clinical decision-making in youth with diabetes.

Conclusion: Confirming a diagnosis of MODY requires proper knowledge of the key features of the disease and its genetic mode of inheritance, a reliable family history, and predilection of race and phenotype. Because treatment options, outcomes, and genetic counseling differ in MODY compared to T1D and T2D, whenever appropriate clinicians should consider performing genetic testing. Using a diagnostic algorithm for children presenting with dysglycemia will provide physicians a cost-effective way to decide which patients may benefit from genetic testing and, hopefully, reduce the frequent misdiagnosis of MODY. Further studies are needed to determine the utility of the proposed model.

Sponsor: Cook Children's Medical Center

IRB/IACUC#: CCHCS-IRB
Diagnosing Autism Spectrum Disorder in Adolescents: The Value of Screening in Late Infancy into Early Adulthood

Autism Spectrum Disorder (ASD) is a complex neurological disorder that affects a patient’s ability to interact and socialize with others due to challenges they face with communication and behavior. ASD has become increasingly popular in the healthcare community but still, pediatricians find themselves lacking a standardized screening tool for their patients. At UNTHSC Pediatrics clinic, ASD is screened for at 18 months and 24 months of age by having the parents fill out a form called the MCHAT, or Modified Checklist for Autism in Toddlers. These questions specifically look for behaviors of social misconduct, abrupt reactions to environmental stimuli, situational overreaction and decreased emotionality, speech or eye contact issues, or the occurrence of repetitive behaviors. However, after 24 months of age, children with negative MCHATs are no longer screened for ASD even though as a child ages they can present more clearly with signs of ASD. ASD is commonly mistaken for multiple other psychological or neurodevelopmental disorders including but not limited to ADHD, OCD, anxiety, and depression. In this case study, we address the importance of screening in late infancy up through early adulthood by showing a case of misdiagnosis of ADHD in a patient with ASD. We will present tools and recommendations for pediatricians to use in evaluating patients for possible ASD.

Sponsor: N/A
IRB/IACUC#: 2017-091
Are Patients with Adrenal Insufficiency and X-linked Adrenoleukodystrophy Substrate-Limited?

BACKGROUND

X-linked adrenoleukodystrophy (X-ALD) results from inherited defects in the ATP-Binding Cassette Subfamily D Member 1 gene (ABCD1), which encodes adrenoleukodystrophy protein (ALDP), a peroxisomal protein involved in intracellular lipid transport. X-ALD phenotypes include various combinations of cerebral, neurological, and adrenal abnormalities, with up to 70% of affected males demonstrating primary adrenocortical insufficiency (AI). The pathogenesis of X-ALD is largely attributed to the accumulation of very long chain fatty acids (VLCFAs). It has been suggested that impaired intracellular transport of cholesterol may also play a role in the pathogenesis of AI in X-ALD. The objective of this case study is to review the mechanisms of cholesterol transport and availability in steroidogenic cells in patients with X-ALD who develop AI.

CASE INFORMATION

A 27-month-old male was referred for evaluation of adrenal function following a diagnosis of X-ALD. Serial laboratory results revealed progressive decline of both baseline and stimulated adrenal function.

DISCUSSION

In steroidogenic cells, cytosolic free cholesterol is incorporated into the outer mitochondrial membrane (OMM) by a complex of proteins, including mitochondrial transport protein TSPO. Steroidogenic acute regulatory protein transports cholesterol from the OMM to the inner mitochondrial membrane (IMM) where the initial steps of steroidogenesis occur. If cholesterol isn’t available at the IMM, no steroid hormones are produced.

Because cholesterol is critical for steroid hormone synthesis, adrenal cortical cells have redundant mechanisms of cholesterol acquisition to ensure an adequate supply, including from circulating lipoproteins, intracellular stores, and de novo synthesis. Disorders affecting lipid and lipoprotein metabolism—as well as lipid lowering treatments, such as use of statins—could potentially alter adrenocortical function. However, there are few reports of AI in these disorders.

CONCLUSION

Because cortisol is essential for health and the body’s response to stress, redundant mechanisms of acquiring cholesterol allow steroidogenic cells to acquire cholesterol in spite of ALDP deficiency. The inability to process VLCFAs and accumulation of lipids in X-ALD, however, appears to overwhelm the adrenal cortical cells, resulting in cell death and primary AI.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Do Mental Health Levels Differ by Activity Limitations and Physical Activity in Arthritic Males Ages 50-79?

Purpose: Depressive symptoms are a common comorbidity seen with arthritis. Despite previous research showing the effect of activity on depression levels, there has been a lack of research within the older arthritic male population. The purpose of this study was to evaluate whether activity limitations and physical activity are related to mental health levels in arthritic males ages 50 -79.

Methods: This cross-sectional analysis used BRFSS 2015 data for males ages 50-79 from Alabama, Arkansas, Kentucky, Tennessee, and West Virginia. Multiple logistic regression analysis was used to assess the relationship between activity limitations and physical activity with mental health, while controlling for general health, health care access, weight status, race, educational level, and income level.

Results: Less than one-third participants reported less than good mental health (27-31%), approximately half reported activity limitations (47-53%), and over half of participants reported their activity level as inactive/insufficiently active (52-58%). Adjusted results indicated that activity limitations were significantly related to mental health (moderate effect sizes) in all five states, but physical activity was only significant in one state. In addition, cost precluding seeing a provider was found to be significant.

Conclusions: Overall, mental health was found to be significantly related to activity limitations and healthcare access in all five states, but not to physical activity levels. Therefore, male arthritic patient ages 50-79 in a primary care setting should be screened for both mental health issues and activity limitations if they present with symptoms of either. In addition, primary care clinics that are in lower socioeconomic (SES) areas should take into account the effect that cost has on mental health and activity limitations in arthritic patients when developing treatment plans.

Sponsor: N/A
IRB/IACUC#: 2017-070
LAM- A Post-Op Hypoxia Dilemma

Background/Abstract:

Lymphangioleiomyomatosis (LAM) is a rare multisystem disease that mostly affects young women. It is estimated that approximately 3 to 5 out of every 1 million women are affected. The primary histopathological abnormality is the proliferation of atypical smooth muscle-like cells. The most common presentation of LAM is signs and symptoms of lung disease, however, patients can also present with extrapulmonary manifestations such as renal and lymphatic disease. Lymphangioleiomyomas are lymphatic fluid filled benign tumors found in the pelvic, retroperitoneum, and mediastinum that occur in 16 to 38 percent of patients with LAM. Here we present a case of a young female with no past medical history who presented for elective surgical removal of a pelvic mass. The hypoxia present during the postoperative course led to the diagnosis of LAM.

Case Report:

A 31 yo Caucasian female with no significant past medical history presented to our hospital for elective surgical removal of a pelvic mass. The operative course was unremarkable. Patient was extubated to nasal cannula after the surgery, but was unable to maintain oxygen saturation on room air. She was found to be hypoxic, requiring at least 2L nasal cannula to maintain saturation levels in the low to mid 90s. Initial chest X-ray was remarkable for bilateral mild interstitial opacities and bibasilar atelectasis. Despite aggressive incentive spirometry use, patient could not overcome the hypoxemia without supplemental oxygen. CT chest was obtained and showed cystic changes diffusely throughout both lungs. The diagnosis of LAM was considered high on the differential at this point. The patient was discharged on supplemental oxygen and advised to follow up in the pulmonology clinic. Two days after discharge, the pathology from the pelvic mass resulted and was consistent with lymphangioleiomyoma.

Discussion/Conclusion:

This case was unique in the fact that it presented as an extrapulmonary manifestation of LAM that eventually led to the diagnosis of the pulmonary disease. Due to the postoperative nature, atelectasis was initially implicated for the hypoxia in this young female with essentially no prior past medical history, clouding the possibility of other differentials such as LAM. However, in a female with pelvic mass of unknown etiology and pulmonary symptoms, LAM should stay at the top of the differential, despite the rarity of the condition.

Sponsor: N/A
IRB/IACUC#: MCFW-IRB
A Rare Case of Superior Vena Cava Syndrome caused by long-term indwelling Hemodialysis Catheter Placement

Background/Abstract:

End-stage renal disease (ESRD) cases continue to rise at approximately 21,000 cases per year in the US.1 During the past decade there has been a trending increase in use of central venous catheters (CVC) for hemodialysis (HD).2-3 When inserted into the superior vena cava (SVC), these catheters have been shown to be associated with thrombosis. While malignancy is the most common cause of superior vena cava syndrome (SVCS), an increasing incidence of benign causes are appearing. A portion of these benign causes are associated with the increasing use of intravascular catheters.2,4

Case Report:

A 51-year-old african american female with past medical history of ESRD on HD, type II diabetes mellitus, coronary artery disease, paroxysmal atrial fibrillation who presented to our emergency department with acute neck swelling associated with hoarseness and headache. She states she woke up on the morning of admission with diffuse bilateral neck swelling that increased in size throughout the day. She denied difficulty with swallowing solids or liquids. She also denied difficulty with respiratory effort, chest pain, or shortness of breath. Her Vitals were stable. Clinical exam showed minimal facial edema but prominent superficial veins of the chest wall and neck region. Chest x-ray showed widening of the mediastinum. Our initial clinical impression was cellulitis, angioedema, or allergic reaction. Chest CT showed a thrombus partially occluding the SVC with severe stenosis at the cavoatrial junction. The patient was diagnosed with SVCS and underwent recanalization with angioplasty and stenting of SVC. The symptoms of superior vena cava syndrome began to improve immediately after the angioplasty and she continued to be free of symptoms and was subsequently discharged home. Of note, the patient had a long history of CVC access with repeated and prolonged placement after failed AVGs.

Discussion/Conclusion:

SVC syndrome is a medical emergency and can be fatal if resulting in severe cerebral edema and cerebellar herniation. A slower development of SVC is often better tolerated as many patients develop collateralization of vessels.4 It is thought that approximately half of central vein stenosis remain asymptomatic with clinical manifestations presenting due to eventual local upstream hypertension. In addition to risk of thrombosis of all CVCs, hemodialysis related CVCs are believed to have increased risk of thrombosis due to having longer, thicker lumens and longer length of placement.5-6 Therapy is generally endovascular or surgical with the former fairing better in hemodialysis patients with multiple comorbidities.7 This case illustrates the unusual manner in which SVC can present along with the potential for iatrogenic causes of SVC syndrome. Given the increasing frequency of intravascular
catheter placement, it’s important to identify iatrogenic causes. Avoiding long term use of hemodialysis catheters and timely creation of AVFs may help prevent these complications.

**Sponsor:** N/A

**IRB/IACUC#:** MCFW-IRB
Neuroleptic Malignant Syndrome caused by Cyclobenzaprine

Background/Abstract:

Neuroleptic malignant syndrome is a disorder characterized by a triad of fever, muscle rigidity and altered mental status and classically associated with dopamine antagonists. It is rare and potentially fatal if not diagnosed and treated in the correct manner. There is no specific diagnostic test to rule in the disorder and a high suspicion and detailed list of home medications are needed as it is essentially a clinical diagnosis. A patient's course usually begins with muscle rigidity followed by a fever within several hours, as well as mental status changes that range from drowsiness, agitation, or confusion to a severe delirium or coma. Here we present a unique case of a patient with NMS secondary to cyclobenzaprine. To our knowledge, it is only the third case reported in literature.1-3

Case Report:

A 70 year old male with a past medical history of left-sided ischemic stroke, hypertension, type II diabetes, and chronic back pain presented to our emergency department with altered mental status (AMS). His last known normal was the previous evening around 10pm where the wife admitted to a verbal argument over the patient's frequent overuse of prescribed Norco and Flexeril for his chronic back pain. Upon waking up the following morning the patient's wife immediately noticed AMS, unsteady gait, and loss of bladder control. Upon arrival to our ED the patient was febrile with a max temperature of 104.9, profusely diaphoretic, tachypneic, tachycardic, with muscle rigidity. Pupils were equal and reactive and reflexes were intact. The patient's altered mentation and labored breathing continued to decline requiring intubation and mechanical ventilation. Computed tomography and magnetic resonance imaging of the brain were normal. Continuous EEG was negative for seizure activity. CSF analysis, blood, and urine cultures were negative for infection. Creatine kinase was elevated at 1,963 U/L and WBC elevated at 21.9 k/mm3. Urine triage screen was positive for opiates. The patient was treated with dantrolene and lorazepam with good response in temperature. Slowly, over the course of the next few days, the patient’s symptoms resolved and he was weaned of the ventilator and eventually discharged with no complications.

Discussion/Conclusion:

Our patient's clinical presentation and diagnostic work-up were classic for NMS. Treatment is largely supportive including cessation of the offending agent and pharmacologic interventions in more severe cases such as ours. NSM is thought to be caused by abrupt dopamine receptor blockage and the typical causative agents are antipsychotics. NMS caused by cyclobenzaprine is extremely rare and to the best of our knowledge only two other case reports have been reported in literature. While our case points to an overdose as the most likely pathogenesis, other reports have described a possible idiosyncratic reaction, i.e., immune-mediated reactions that occur rarely and in unpredictable fashion among the population.
This case questions if medications other than antipsychotics such as muscle relaxers should be kept in mind when working up a cause for NMS. The fact that a muscle relaxant can actually potentiate muscle rigidity makes this a unique phenomenon and we feel it should be further investigated.

**Sponsor:** N/A  
**IRB/IACUC#:** MCFW-IRB
Cirrhotic Portal Hypertension: A Case Report

Background: Portal hypertension (PH) is defined as an abnormal increase of the blood pressure in the hepatic portal vein system. PH can result from pre-hepatic, intra-hepatic, and post-hepatic causes with 90% of cases in the United States being due to the intrahepatic cause of cirrhosis. Prognosis of PH is made through calculation of the Hepatic Venous Pressure Gradient (HVPG) via hepatic vein catheterization. Once PH is identified, bleeding and fluid status must be appropriately managed using pharmacological and surgical therapy to avoid complications such as ascites and splenomegaly. In this report, we offer a summary of the diagnosis and management of PH, and present the case of a 59-year-old male diagnosed with the cirrhotic form of PH.

Case Information: This case was selected and assembled using electronic medical records and imaging results. A 59-year old male presented to a family medicine clinic with a chief complaint of abdominal pain for 2 months. Past medical history was significant for chronic hepatitis C, alcohol abuse, and cirrhosis of the liver. An abdominal ultrasound was ordered and revealed morphologic changes of cirrhosis present with evidence of portal venous hypertension with moderate splenomegaly present. Laboratory blood works showed ALT to be 56 U/L (9-46 normal), AST 57 U/L (10-35 normal), GGT 151 U/L (3-85 normal). Otherwise, blood cell counts were within normal limits.

Conclusions: Portal Hypertension (PH) is a serious chronic hepatic illness that can occur due to a variety of pre-hepatic, intrahepatic, and post-hepatic causes. The patient’s PH etiology comes from the most common cause of PH, cirrhosis, which causes around 90% of PH in the United States. In this case, the patient’s cirrhosis was due to hepatic remodeling due to alcohol abuse and hepatitis C. While the definitive way of diagnosing PH remains HVPG, the patient’s symptoms coupled with abdominal ultrasound evidence were enough to make the diagnosis. The patient risks complications involving ascites, further problems with existing splenomegaly, and development of varices. To effectively prevent these complications, careful interdisciplinary medical management must be followed.

Sponsor: N/A
IRB/IACUC#: 2018-042
Residents/Fellows' Perception on Primary Prevention of Premature Cardiovascular Disease

Purpose: Cardiovascular disease is the leading cause of death globally with 6.3 million premature deaths annually. Minimal research has been done on the perception of physicians on primary prevention that may or may not lead to improved disease outcomes. The purpose of this study was to evaluate the perceptions of residents/fellows from different specialities and levels of training. Our hypothesis is that perception of family medicine (FM) and internal medicine (IM) residents on the role of primary prevention in premature cardiovascular disease is greater than surgery and medicine subspecialty (MS).

Methods: Residents/fellows (30 FM, 30 IM, 12 surgery, 6 gastroenterology, & 10 cardiology) from Medical City Fort Worth (MCFW) Hospital were recruited to complete a voluntary, anonymous survey including health care opinions. Inclusion criteria were new/returning residents & fellows at MCFW who consented to participation. Exclusion criteria included those who opted to not participate. Chi square test and logistic regression yielded odds ratio (OR), confidence intervals, and p-values.

Results: There were 56 participants (39% FM, 32% IM, 11% surgery, & 18% MS). The remaining 32 met the exclusion criteria, resulting in a smaller sample size that may affect statistical significance. A confounding factor was the predominance of osteopathic physicians; allopathic residents included: FM (1 PGY2, 1 PGY3) and IM (1 PGY2, 7 PGY1). IM (OR .97), surgery (OR .50), and MS (OR .69) were less likely to identify primary prevention as the best way to eradicate premature cardiovascular disease than FM (p < 0.05). FM was more likely to recognize that more can be done to reduce premature cardiovascular disease through primary prevention than other methods compared to IM (OR 0.81), surgery (OR 0.41), and MS (OR .57) (p < 0.05). FM significantly perceived that patients must be willing to share the responsibility of health with the physician if premature cardiovascular disease is to be prevented versus IM (OR .94), surgery (OR .32), and MS (OR .55) (p < 0.01).

Conclusion: FM residents practice primary & disease (premature cardiovascular disease) prevention and patient involvement more than other specialties. Further research is needed to investigate how perceptions of physicians-in-training, regardless of specialty, directly affect patient lifestyle management & preventive counseling; and whether implementing a lifestyle curriculum can influence perceptive outcomes & primary care.

Sponsor: N/A

IRB/IACUC#: MCFW-IRB 2017.027 (FTW)
Is Obesity a Risk Factor for Depression in Males 55 and Older?

Purpose: Obesity has been associated with many health conditions, including an increased risk of depression. In the U.S., middle aged and older adults are more likely to be obese; however, the relationship between depression and obesity in older adult males is not well understood. Thus, the purpose of this study was to assess the relationship between depression and obesity in elderly men.

Methods: This cross-sectional analysis used 2015 BRFSS data for males aged 55 and older from Oklahoma, Oregon, Tennessee, and West Virginia. Multiple logistic regression analysis was used to assess the relationship between depression and obesity while controlling for: health conditions, activity limitations, age, ethnicity/race, education level, marital status, and metropolitan status.

Results: Overall, approximately one-fifth of participants reported ever being diagnosed with depression or dysthymia (15-20%) and about one-third reported being obese (31-38%). After controlling for health and sociodemographic factors, depression was not significantly related to obesity in three out of four states. However, depression was significantly related to activity limitations (large effect size) and having two or more health conditions in all four states (large effect size).

Conclusions: Depression was not related to obesity in men aged 55 and older, but was significantly related to activity limitations and having two or more health conditions. Limitations to this study include self-reported BMI which is subject to reporting error. Additionally, depression data was measured as lifetime incidence of depression or dysthymia, whereas BMI reflected current weight status. Clinicians should be informed on both depression and obesity in order to screen and educate elderly male patients. Because the two conditions are not related in this population, it is not indicated that practitioners evaluate for one due to the presence of the other. However, if a patient presents with activity limitations or two or more health conditions, it is recommended the practitioner screens for depression, and vice versa.

Sponsor: N/A
IRB/IACUC#: 2017-070
Relationship Between Child Gender and Parental Awareness of the HPV Vaccine

Purpose: While human papillomavirus (HPV) affects both boys and girls, the vaccination rate between the two genders differs. Literacy regarding the HPV vaccine plays a role in vaccination status and parental literacy may influence the variable nature of vaccination rates between boys and girls. This study was designed to assess the role of gender bias in parental vaccine literacy. We believe that parents with daughters will have increased knowledge regarding the HPV vaccine compared to parents with sons.

Methods: Data were collected from 53 participants at the UNTHSC Patient Care Center Pediatric Department. Parents were asked to complete a survey regarding the HPV vaccine and were educated about the vaccine after completing the survey. A flyer with information about the vaccine was given to the participants who were called approximately 10 days after completing the survey to gauge retention of information. Data was assessed using a chi-squared analysis for possible connections between child gender and the accuracy of survey answers.

Results: 81% of parents of female children (POFC) answered that they understood how HPV was spread compared to 72% of parents of male children (POMC). 44% of POMC and 39% of POFC were unsure about whether condoms fully protect against HPV. Only 52% of POMC correctly answered that there is an HPV vaccine for boys compared to 74% of POFC. 35% of POMC reported having a healthcare provider speak to them about the HPV vaccine compared to 44% of POFC.

Conclusions: Both sets of parents displayed variable understanding regarding different aspects of HPV and the HPV vaccine. POMC displayed a greater lack of understanding about how HPV is spread as well as the incorrect belief that HPV is spread only through sexual contact. POMC were also less likely to be aware of a male HPV vaccine. This variance in knowledge may indicate that there is a reduced likelihood that POMC will learn about vaccines from healthcare providers compared to POFC. Misbelief among POMC as well as a lack of education from providers could play a role in reduced vaccination rates among boys. Future studies should investigate the need for unique training for providers regarding speaking with POMC about the HPV vaccine.

Sponsor: N/A
IRB/IACUC#: 2015-148
Does General Health Differ by Healthcare Access in Diabetic Females 30-50 Years of Age?

Purpose: Diabetes is one of the fastest growing epidemics requiring regular medical management, yet 12.6% of U.S. adults were without health coverage in 2015 (1,2). Our study aims to determine whether general health differs by healthcare access in diabetic females 30-50 years of age.

Methods: This cross-sectional analysis used data from the 2015 BRFSS for females ages 30-50, from Louisiana, Mississippi, Oklahoma, and Tennessee. The relationship between general health to healthcare access and healthcare cost was analyzed using multiple logistic regression analysis controlling for weight status, comorbid conditions, age, ethnicity, marital status, income, education level, and state.

Results: A high prevalence of participants reported having healthcare coverage (80%) and a moderate prevalence reported good or better overall general health (60%). There is a significant inverse relationship between healthcare cost and general health (OR=0.55, 95% CI=0.31, 0.97). There was no significant relationship between healthcare access and general health outcome. Additionally, relationships were shown between general health and comorbid conditions (OR=0.08, 95% CI=0.02, 0.27), income (OR=2.54, 95% CI=1.44, 4.45), and education level (OR=1.97, 95% CI=1.06, 3.66).

Conclusions: Results show a significant relationship between healthcare cost, comorbidities, education, and income to participant’s general health. However, healthcare coverage was not significantly related to participant’s general health. Results may be utilized in primary care practice settings managing diabetic females aged 30-50. This population of patients should be screened for poor general health and additional comorbid conditions in low socioeconomic patient populations.

Sponsor: N/A
IRB/IACUC#: 2017-070
Effects of Cognitive Impairment on Hospitalizations in Heart Failure Patients

Purpose: Heart failure (HF) is a major health problem in the United States (US) linked to poor survival rates, high rehospitalization rates and high healthcare cost. HF is positively associated with aging and its impact on US health and healthcare systems is expected to grow as the baby boomer generation enters their retirement years. The same is true for another chronic health risk, cognitive impairment. There is a clear, negative impact on prognosis and healthcare outcomes associated with cognitive impairment in HF patients, but less is known about how these affect systems outcomes such as overall hospitalization. We compared hospitalization patterns among aged HF patients with and without comorbid cognitive impairment to identify associated risks and outcomes.

Methods: The data for this analysis will be obtained from the Medical Expenditure Panel Survey. MEPS is a survey that is conducted each year through the Agency for Healthcare Research and Quality (AHRQ) including both a household and an insurance component. MEPS provides relevant data including number of hospital discharges, diagnosis codes, etc. The sample is a stratified, cluster sample to ensure racial representation.

Statistical analyses will be performed using SAS. Estimates of risk of hospitalization for patients with and without cognitive disorders will be calculated using self-response weights. Associated standard errors will be calculated using replicate weights obtained from MEPS. For the first question, differences in the distribution of risk for patients with and without cognitive disorders will be evaluated using weighted Chi-squared tests. A weighted logistic regression will be used to find factors associated with hospitalization risk by examining associations among demographic and other characteristics with the outcome. Goodness-of-fit of the model will be assessed using the Hosmer-Lemeshow test and a deviance test.

Results and Conclusions: pending

Sponsor: N/A
IRB/IACUC#: 2018-022
Effects of the Motion Wellness System on balance, coordination, strength and quality of life in older adults: a survey study

PURPOSE: The purpose of this study is to investigate the benefits of the Motion Wellness Platinum Systems equipment, the patterns of usage of the equipment, and the related factors facilitating and impeding usage of the equipment.

METHODS: The study will take place over a one year period, November 1, 2016-October 31, 2017. Data will be collected from users aged 55 and older at all 3 Motion Wellness System sites in Fort Worth and Arlington. Surveys will be collected for a duration of 6 months with an average data collection of 2 hours per site visit. Number of users during the data collection visits at each site and total number of users of the equipment over the period of data collection will be recorded, regardless of whether people agree to complete the survey or not.

RESULTS: During the data collection period, in 36.5 hours of data collection, only 5 users matched the targeted age group and agreed to complete a survey. Fifty-one people used the equipment, mostly consisting of children who were accompanied by adults less than the age of 55. Through the survey, factors that facilitated usage included newspaper/magazine advertisements informing the community about the installation of the Motion Wellness System. Factors that impeded usage included the presence of too many children using the equipment and participants’ lack of transportation.

CONCLUSION: The awareness or cultural acceptance of adult playgrounds is not as strong in the western civilization as it is in Asian countries. Lack of advertisement about the Motion Wellness System and the benefits of exercise within the area possibly resulted in the less-than-expected turnout. Location is another limitation to this study. The initial proposal stated to construct equipment near senior centers where older adults can freely use the system and perhaps even participate in group exercises using the system. Even if older adults wanted to “play” on the playground, they were likely to shy away in presence of the children, the majority of users. In addition, during the first month of data collection, the frequent rain and occasional high temperatures discouraged outdoor activities. Overall, the benefits of the Motion Wellness System, the patterns of usage, and the factors facilitating and impeding usage are inconclusive due to the small sample size in this study.

Sponsor: North Texas Specialty Physicians Charitable Fund
IRB/IACUC#: 2016-164
Is Heavy Alcohol Use Related to Chronic Health Conditions in Middle-aged Adults?

Purpose: Previous research has studied the detrimental effects of heavy alcohol use on a person’s health, but little research has focused on its relationship with the number of health conditions that occur as a result. The purpose of this study was to determine the relationship between heavy alcohol use and number of chronic health conditions in middle-aged adults 35-54 years old.

Methods: This cross-sectional analysis used 2015 BRFSS data for middle-aged adults 35-54 years old from Alaska, Maine, Missouri, and Wisconsin. Multiple logistic regression analysis assessed the relationship between alcohol use and the number of chronic health conditions while controlling for age, weight status, healthy eating, education level, healthcare access, income level, marital status, ethnicity/race, gender, and tobacco use.

Results: Alcohol use was common with 33-40% of participants reporting as moderate drinkers, and 18-34% reporting as heavy drinkers. In addition, having multiple chronic health conditions was moderately prevalent with 35-47% of participants reporting having 2 or more. After controlling for social behaviors and demographic factors, heavy alcohol use was significantly and inversely related to the number of chronic health conditions in three out of four states (small to moderate effect sizes). Also, in three out of four or all four states income level was also inversely related (moderate to large effect sizes), while tobacco use, weight status, healthcare coverage, and older age were positively related to number of chronic health conditions (low to large effect sizes).

Conclusion: Overall, current heavy alcohol use had a significant and inverse relationship to the number of chronic health conditions in general population samples of middle aged adults. It is recommended for practitioners to continue to follow standard screening protocols for alcohol use in a primary care setting for middle-aged adults. If the patient screens positive for heavy alcohol use, then practitioners should screen for multiple chronic health conditions. Similarly, if a patient presents with multiple chronic health conditions, practitioners should screen for alcohol use.

Sponsor: N/A
IRB/IACUC#: 2017-070
Implementation of the HomeMeds Medication Management System in a Primary Care Setting

Purpose: HomeMeds, an electronic medication management system, has been shown to prevent and reduce adverse effects of medications in the elderly by reconciling medications and looking at cardiovascular, psychotropic, nonsteroidal anti-inflammatory drug (NSAID), or duplication problems. The program was originally designed and tested for use in a home setting, but less is known about use in a primary care setting, and few studies can link the intervention to patient health outcomes.

Methods: A retrospective analysis was performed on data from January – June 2017 of patients (n=300) 65 years and older in our electronic medication record (EMR) and from a Center for Disease Control (CDC) validated “Healthy Days” questionnaire administered by Meals on Wheels Inc (MOWI) of Tarrant County at a primary care geriatric clinic. The questionnaires examined physical and mental health and history of falls and hospitalizations, while the EMR provided Activities of Daily Living/Independent Activities of Daily Living (ADL/IADL) scores and demographic data. In addition to frequencies, odds ratios (OR) with 95% confidence intervals (CI) were estimated in a logistic regression analysis. Chi square tests compared groups.

Results: The mean age was 77.63 years with 77% being female, and the mean number of medications per person was 11. Of those with alerts (n=210), the mean number of alerts per person was 2, with the most common being duplicate therapies (n=148) and 26% reported a fall history while 41% reported dizziness. The odds of reporting dizziness and a previous fall is 3.7 times higher compared to those without a previous fall. The odds of having a previous fall is 2.4 times higher for those reporting a lower health status (X²=8.433, df=1, p=0.004). Females had a higher proportion and were more likely to generate an alert than males (X²=5.679, df=1, p=0.017). The odds of having an alert are increased, but not statistically significant, for clients with low ADL/IADL scores and nonwhite (p=0.144, p=0.078, p=0.281).

Conclusions: If patients are able to change or remove a medication predisposing them to dizziness, perhaps fall risk can be reduced. With the rising elderly population and the elderly’s increased frailty, this could be potentially life-saving. The primary care physician shortage and increasing elderly population make it more crucial than ever to improve patient health and HomeMeds is a feasible and relatively simple way to do just that.

Sponsor: N/A
IRB/IACUC#: 2017-085
Association of Nutritional Label Literacy and Eating Habits in Adult Population of Rural Texas

Purpose: The Nutrition Facts panel (NFP) (nutrition labels on food packaging) is one of the best ways to disseminate nutritional information at the point-of-purchase to help reduce total calorie intake and sodium, saturated fat, trans fat, cholesterol, and added sugar consumption. Purpose of this study was to examine the association between the ability to interpret nutrition labels correctly and eating habits in the adult population in rural Texas.

Methods: A total of 121 adult subjects were recruited from five primary care clinics located in rural Texas. Data on nutrition label literacy and dietary practice were collected using the Newest Vital Sign and the NHANES Dietary Screener Questionnaire, respectively. Univariate analyses and regression analyses were carried out to estimate the strength of association between nutrition label literacy and eating habits.

Results: About one-fifth of the subjects had very low nutrition label literacy. Only two-thirds of the subjects were able to calculate the percentage daily value of calories in a single serving. After adjusting for the demographic variables, higher educational level (OR = 3.53), higher income (OR = 5.10), and lower amount of added sugar consumption (OR = 1.14) were found significantly associated with a higher level of nutrition label literacy.

Conclusions: Adult population in rural Texas had difficulty in interpreting nutrition label correctly. This study supported the hypothesized linkage between the ability to interpret nutrition labels and healthy eating practices. Revision of the NFP to reduce complexity and account for varying levels of literacy should be considered for future nutrition labels.

Sponsor: N/A
IRB/IACUC#: 2017-058
Adenosine Triphosphate (ATP) monitor gauges for testing and validation of biological laboratory disinfection process.

Purpose: Many University of North Texas Health Science Center (UNTHSC) laboratories work with microbiological organisms, which without enough safety precautions or if inappropriately contained, may lead to harmful diseases to the people working in the laboratories. The presence of these organisms on the working stations of the laboratory personnel infers improper disinfection of the surfaces which might lead to a possible exposure and deleterious health effects leading to lawsuits. Therefore, the study aims at detecting these microorganisms using an Adenosine Triphosphate (ATP) monitor.

Methods: The study involves the use of the ATP monitor which gauges the presence of a biological agent at any surface and has mostly been used in the food industry for maintaining the quality of food. It has not yet been used in laboratory settings and is going to be tested for its efficacy in such an environment for the first time in UNTHSC labs. As it is an intervention of its kind, the process involves the identification of the labs using biological agents through an annual laboratory inspection and later using the ATP monitor on surfaces coming in frequent contact with people using those particular labs.

Results: The results obtained after analysis of the data gathered by the ATP monitor would be used to establish a baseline level of cleanliness and decontamination for laboratories and create a periodic testing protocol to maintain the established levels.

Conclusion: The research-oriented laboratories on the UNTHSC campus are of Biosafety Level (BSL) 1 or 2 which implies that they work with several pathogenic organisms which pose a moderate risk to human health. Using an ATP monitor seems to be a promising approach towards enhancing the biosafety on the campus and maintaining a good validation process for laboratory disinfection, thus keeping the environment a safe area to conduct research.

Sponsor: N/A
IRB/IACUC#: N/A
Factors Associated with Patient Satisfaction in a Pediatric Setting Based on a Newly Developed Survey Instrument

Purpose: Patient’s satisfaction has been shown to play a major role in their perception of the overall quality of care they receive. In a pediatric setting, caregiver’s satisfaction acts as a proxy for patient’s satisfaction. While there are a limited number of survey instruments that are designed to assess patient satisfaction in a pediatric clinic setting, none have examined an academic pediatric setting. In this study, there were two goals: first, to design a survey instrument to measure patient satisfaction in an academic pediatric setting and collect data using that instrument; second, to measure associations between patient’s satisfaction and factors such as provider’s ability to communicate effectively and receiving timely access to care.

Methods: A paper-based survey instrument consisting of 44 questions was developed using a validated instrument for patient satisfaction as reference, and included additional questions pertinent to an academic setting. Data was gathered from 97 caregivers over the age of 18 years, through convenience sampling, at the UNT Health Science Center Health Pavilion Department of Pediatrics. Patient satisfaction was assessed using the question “Using any number from 0 to 10, where 0 is the worst provider possible and 10 is the best provider possible, what number would you use to rate this provider?”. The reliability of the instrument was measured by Cronbach’s alpha. Descriptive statistics were used to describe the sample. Logistic regression was used to model patient satisfaction, after converting it into a binary variable where satisfaction ≤ 8 was ‘low/medium satisfaction’ and > 8 was ‘high satisfaction’.

Results: Cronbach’s alpha was 0.55. Median provider satisfaction was 10 (IQR=3). Controlling for other factors in the model, as provider communication score increased by 1 unit, the odds of being in the low/middle category decreased by 0.01 (p)

Conclusions: The low Cronbach’s alpha indicates that the instrument development requires further investigation and re-evaluation. The small sample size and missing data may have contributed to this lowered score. Based on study results, we conclude, with caution that patient satisfaction was significantly associated with provider communication and receiving timely access to care.

Sponsor: N/A
IRB/IACUC#: 2017-125
Prescribing Practices Related to Concomitant Opioid and Benzodiazepine Use: A Focus Group

Purpose: The Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) have issued warnings against the co-prescribing of benzodiazepines and opioids due to increased risk of drug overdose. Despite these warnings, benzodiazepines remain commonly prescribed with opioid containing products. The factors behind this practice are not well described. The objectives of this study were to evaluate provider perceptions in the following areas related to concomitant opioid and benzodiazepine use: prescribing practices, mitigation of patient risks, and issues not addressed by other agencies.

Methods: This study was approved by the University of North Texas (UNT) Health Science Center in November 2017. Focus groups were conducted among providers at UNT Health clinics in Fort Worth, TX, to elicit opinions related to the co-prescribing of opioids and benzodiazepines. The study investigators co-identified themes after the focus groups. Open coding was performed for the initial thematic analysis, followed by selective coding upon theme identification. Descriptive statistics were used to characterize demographic information from study participants.

Results: A total of 6 subjects were interviewed thus far; 3 (50%) males, 3 (50%) Asian, median age in years 39.5 (IQR 33-46.8), and median number of years in practice 12 (IQR 5.9-17.8). Four (67%) self-identified as attending physicians, and 2 (23%) self-identified as pharmacists. Major themes identified include “Providers are cognizant of risks of concomitant opioid and benzodiazepine therapy but may not have changed current practices,” “Common barriers to deprescribing therapy include patient preference and lack of resources (e.g., behavioral health),” and “Negative outcomes include adverse effects and inappropriate use.” Provider resources to mitigate patient risk include the Opioid Risk Tool, prescription monitoring programs, and practice-based quantity limitations. Additional data will be reported at the 2018 Research Appreciation Day.

Conclusions: Preliminary results suggest that providers are aware of the risks associated with concomitant opioid and benzodiazepine therapy but face a number of challenges in tapering or discontinuing therapy. These findings may be used to impact trainee education and clinical practice. Final results and conclusions will be presented at the 2018 Research Appreciation Day.

Sponsor: N/A
IRB/IACUC#: 2017-151
The Association Between Enrollment in the Supplemental Nutrition Assistance Program and Household Food Security Status

Purpose: Food insecurity, or not having reliable access to nutritious food, is a problem that many U.S. families face today. The Supplemental Nutrition Assistance Program (SNAP) provides a monthly benefit to low-income individuals. Recent research has reported inconsistent findings about the effectiveness of SNAP in reducing food insecurity. This study examined the association between SNAP enrollment and household food security status.

Methods: This cross-sectional study was conducted using data from the National Health and Nutrition Examination Survey (NHANES) 2013-2014. Logistic regression was used to model food security status predicted by SNAP participation while adjusting for the effects of age, gender, race/ethnicity, country of birth, education level, federal poverty ratio, and body mass index. All analyses were conducted using SAS 9.4 with appropriate survey weighting procedures.

Results: Hispanics [OR = 2.189, (95% CI: 1.212 - 3.954), p < 0.01], non-Hispanic Blacks [OR = 1.645, (95% CI: 1.208 - 2.242), p < 0.01], and other races [OR = 1.901, (95% CI: 1.120 - 3.226), p < 0.02] were more likely to be food insecure. Older individuals [OR = 0.187, (95% CI: 0.101 - 0.346), p < 0.0001] and individuals with a college degree [OR = 0.257, (95% CI: 0.113 - 0.535), p < 0.0002] were negatively associated with food insecurity. SNAP participation was positively associated with food insecurity [OR = 2.306, (95% CI: 1.806 - 2.946), p < 0.0001].

Conclusion: The measured demographic characteristics were consistent with existing literature and with conventional expectations; however, the finding that SNAP participation was positively associated with food insecurity was unexpected and inconsistent with the literature. Some research has suggested that the once-per-month distribution schedule of SNAP allows participants to deplete their benefits by the middle of the month, providing for a cyclical pattern of relative food security during the first half of the month and relative food insecurity during the last half of the month. Longitudinal research should be conducted to further analyze the strengths and limitations of SNAP as a tool to reduce food insecurity in the U.S and compare its effectiveness to other nutrition assistance programs.

Sponsor: N/A
IRB/IACUC#: 2017-104
Is alcohol use related to high cholesterol in premenopausal women aged 40-51 years old?

Purpose: Alcohol use and cholesterol are related in men and postmenopausal women but relations between alcohol use and cholesterol are unclear for premenopausal women. The purpose of this study was to determine whether alcohol use was related to cholesterol in women aged 40-51 years old.

Methods: This cross-sectional analysis used 2015 data from the Behavioral Risk Factor Surveillance System (BRFSS) for females aged 40-51 years old from Louisiana, Michigan, Nevada, and Tennessee. Multiple logistic regression analysis was used to assess the relationship between high cholesterol and alcohol use while controlling for high blood pressure, diabetes, weight status, daily fruit and vegetable intake, physical activity, tobacco use, age, and ethnicity/race.

Results: Across states, approximately one-third of women reported being diagnosed with high cholesterol (25-36%) and about half reported any alcohol use (36-55%). The results of adjusted analysis indicated that high cholesterol was not significantly related to alcohol use in three of four states. However, high cholesterol was significantly related to blood pressure in all four states with moderate to large effect sizes, and to weight status and tobacco use in three of four states with moderate to large effect sizes.

Conclusion: The results of this study indicate that high cholesterol is not related to alcohol use in females aged 40-51 years old, but is moderately to highly related to high blood pressure, weight status, and tobacco use. For premenopausal women in a primary care setting, about one-third may have high cholesterol, and because high cholesterol, high blood pressure, overweight or obese, and smoking are moderately to highly related, it is recommended to screen for all four if symptoms of any are present and educate and treat as comorbid conditions.

Sponsor: N/A
IRB/IACUC#: 2017-070
Assessing Caregiver Health Literacy on HPV and the HPV Vaccine Based on Health Provider Communication

Purpose: HPV is an easily spread sexual infection that is a leading cause of cervical cancer and contributes to penile, anal and throat cancer. Despite the high success rate of the HPV vaccine in targeting high risk strains of HPV, the rate of use of the vaccine remains low. This project aims to assess patient literacy about HPV and better understand the misconceptions that keep individuals from becoming vaccinated. We will also examine the role of provider education. The goal is to also increase awareness about HPV and the vaccine.

Methods: Surveys were administered to parents of pediatric patients recruited at the UNTHSC Patient Care Center. After consenting and completing the multiple choice surveys, participants were given a brief education session concerning questions in the survey about HPV and the vaccine. They were also given a handout ‘What you need to know about Human Papilloma Virus (HPV)’ to keep. 10 days later participants were contacted to complete the same “follow up survey” to determine retention of knowledge.

Results: The number of participants that reported prior HPV education by a health care provider equaled the number that denied previous education. On HPV knowledge assessment questions, the number of participants that chose the correct/true statement varied by question and by self-reported HPV education. The group that reported HPV education did not show greater knowledge then the other group.

Conclusion: The facts that there is more than one type of HPV and that there is no cure for HPV are less well known. Although participants demonstrated some correct basic knowledge about HPV and the vaccine, there is a lack of complete understanding regarding the magnitude of the disease and the long term consequences. Further work should be aimed at increasing education and exploring the correlation with vaccine acceptance.

Sponsor: N/A
IRB/IACUC#: #2015-148
Introduction:
The 2015 Dietary Guidelines Advisory Committee (DGAC) is a joint effort between the U.S. Departments of Health and Human Services (HHS) and of Agriculture (USDA). Every five years the committee publishes a report containing dietary information and eating habits involving the American public. This study aims to review the literature utilized by the 2015 DGAC to describe the methods of data collection and selected results pertaining to the pediatric population. It will also present the results of the Youth Risk and Behavior Survey conducted amongst Fort Worth high school students to offer comparative data between local and national benchmarks of pediatric nutrition.

Methods:
A literature review was conducted using the DGAC’s published report index on the www.health.gov website. The primary results were retrieved from the 2007-2010 National Health and Nutrition Survey (NHANES) and the CDC’s Second National Report on Biochemical Indicators of Diet and Nutrition in the US Population. Dietary reference intakes for macro and micronutrients were taken from the Food and Nutrition Board and the Institute of Medicine’s reference manual. Statistics concerning Fort Worth’s population were taken from the Tarrant County Public Health Department and the 2016 FWISD Youth Risk and Behaviors Survey.

Results:
About 1/3 of children are expected to be obese. Concerning fruit intake, children ages 1 to 8 years meet recommended intakes, however average intakes of fruit are lowest among girls ages 14-18 years. Males and females on both national and local levels are receiving fewer servings of fruits and vegetables than advised, and their protein intake is on the lower end of the recommended range. Overall, all age groups and genders intake more sugar and saturated fats than recommended.

Discussion:
The target audience for the published Dietary Guidelines results are medical professionals who then work to translate the findings into usable resources for the public. One of the initiatives set forth by the USDA was MyPlate, an online tool that offers ideas for creating healthy eating recipes that encompass all necessary food groups and proper proportions. A local initiative in Fort Worth with similar focus is the Mobile Pantry program. Further studies can assess the success of such initiatives in fostering healthy eating among children.

Sponsor: N/A
IRB/IACUC#: N/A
For general physical health, is heavy alcohol use related to stroke diagnosis in middle aged women?

Introduction: Stroke and alcohol have been linked in previous research, none have focused on middle aged women. The purpose of this study was to assess whether heavy alcohol use is related to stroke diagnosis in middle aged women.

Methods: This cross-sectional analysis used 2015 BRFSS data for middle aged women, ages 45-64, from Missouri, Louisiana, and Michigan. Multiple logistic regression analysis assessed the relationship between heavy alcohol use and stroke diagnosis while controlling for education level, ethnicity/race, tobacco use, weight status, high blood pressure, and diabetes.

Results: A small percentage of the participants reported ever being diagnosed with stroke (4-6%) and about one-fourth reported heavy alcohol use (21-32%). Results of adjusted analysis indicated that heavy alcohol use was inversely related to stroke in Louisiana (AOR=0.18, 95% CI= 0.04, 0.78) and Michigan (AOR=0.38, 95% CI=0.18, 0.79) but not in Missouri. Furthermore, stroke was significantly related to education level in Missouri and Michigan, and high blood pressure in Louisiana and Michigan.

Conclusion: Overall, heavy alcohol use was found to be significantly and inversely related to stroke diagnosis in middle aged women in two out of three states. Since this data was from a population based study, the results may generalize to patients in the primary care setting. As a result of the inverse relationship, practitioners should only assess middle aged women for stroke if symptoms are present because of the low prevalence in this population. Additionally, because one in four participants reported heavy alcohol use, standard screening and patient education about the health risks associated with excessive drinking should continue to occur.

Sponsor: N/A
IRB/IACUC#: 2017-070
Using Machine Learning Technique to Explore Factors Associated with Change in Quality of Life Among Permanent Supportive Housing Residents

Purpose: The purpose of this study was to identify predictors of change in the overall quality of life (QOL) at 6-months, compared to baseline, among permanent supportive housing residents with a history of chronic homelessness and mental illness.

Methods: Data were collected at baseline and 6-month using 18 questionnaires, encompassing over 100 variables on 457 adults. The short version of the Quality of Life Enjoyment and Satisfaction Questionnaire was used to measure QOL. We used a machine learning technique for dimension reduction to achieve a final predictive model for QOL. We used a two-step approach: first, using a machine learning technique called random forest (RF) for dimension reduction by eliminating unimportant variables, and then using a model selection technique in multiple linear regression (MLR) framework with the reduced set obtained from RF to propose a final model. In the process, we highlighted the utility of RF as a means of exploring the fullness of a dataset in order to identify factors associated with improvement in QOL. We captured the linear relationships only in the final predictive model.

Results: The mean improvement in QOL score at 6-months was 4.24 (SD=13.52, effect size=0.31). Significant predictors of the change in QOL were one’s baseline QOL (estimate=-0.32, p)

Conclusion: QOL is a multifaceted concept that encompasses various constructs ranging across physical health, psychological state of mind, social circumstances, environmental factors, etc. We hope that future interventions addressing QOL in this vulnerable population will benefit from our findings. Methodologically, we illustrate the benefit of using machine learning techniques in behavioral/social experiments to leverage “big data” and conduct comprehensive analyses.

Sponsor: N/A
IRB/IACUC#: 2014-125
Is Arthritis a Risk Factor for Kidney Disease in Females Ages 65 and Older?

Purpose: Previous research has shown a relationship between kidney disease and arthritis, however, the results are not specific to a gender or age group. Thus, the purpose of our study was to determine whether arthritis is a risk factor for kidney disease in females aged 65 and older.

Methods: This cross sectional analysis used data from the BRFSS 2015 survey for females aged 65 and older from Arizona, Kentucky, Oregon and West Virginia. Multiple logistic regression analysis was used to assess the relationship between kidney disease and arthritis, while controlling for weight status, high blood pressure, diabetes, heart disease, high cholesterol and ethnicity.

Results: Few of the target population reported having a lifetime diagnosis of kidney disease (6-8%). The majority of the target population reported having a lifetime diagnosis of arthritis (51-64%). After controlling for extraneous factors, kidney disease was significantly related to arthritis in two of the four states with moderate to large effect sizes. Kidney disease was also significantly related to high blood pressure, heart disease, and diabetes in all four states.

Conclusions: Arthritis was significantly related to kidney disease in females aged 65 and older in two of four states and to high blood pressure, heart disease, and diabetes in all four states. Female patients age 65 and older who have been diagnosed with arthritis or kidney disease should be screened for the other disease. Providers should educate patients on early signs and symptoms of these diseases. Providers should also screen patients for kidney disease and educate patients on early symptoms when patients have high blood pressure, heart disease, and diabetes.

Sponsor: N/A
IRB/IACUC#: 2017-070
A Market-based Approach to Improving Passive Surveillance of Tuberculosis in Tarrant County

Purpose: To explore a new method of public health action to further domestic tuberculosis (TB) elimination efforts through cooperation with private healthcare partners in the Tarrant County, Texas public health catchment.

U.S. efforts towards TB elimination have recently stalled. Research has shown that these efforts should be expanded to include latent TB infection (LTBI). However, limited resources, a vague mandate, and more make it difficult for public health to maintain consistent surveillance and treatment of LTBI. Therefore, a market-based approach is an attractive method for addressing this new focus. Understanding facilitators and barriers is paramount to developing such an approach. Experience from this limited context, a largely urban population of just over 2 million, will inform if and how a market-based approach can contribute to national TB control efforts.

Methods: Interviews and focus group discussions with key individuals from the Tarrant County public health catchment were held beginning 5/19/2017 to explore (1) supporting research, (2) community partners serving at-risk populations, (3) facilitators and (4) barriers.

Results:

(1) Supportive evidence from epidemiology, economics, public health, private healthcare, etc.: potential gross for local providers exceeding $7 million & estimated 14.5% of Tarrant’s 2015 population are high risk.

(2) In Tarrant County, there is one federally qualified healthcare center organization that serves a significant portion of high risk individuals.

(3) Facilitators include partner healthcare organizations, CDC support, provider advocates, etc.

(4) Barriers include costs (real and perceived), changes to clinical and documentation practices, coding/billing, etc.

Conclusions: There is a wealth of evidence to support the feasibility of such a project. Identification of the appropriate at-risk population(s) and their respective healthcare providers highlights community partners likely to be interested in such a project. Through the collection of appropriate resources, use of identified facilitators, and addressing of respective barriers, the project could be implemented at little to no direct cost to the private healthcare organization. Furthermore, the combination of these could yield an effective program that is financially lucrative, thereby meeting the goals of both public health and private healthcare.

Sponsor: CDC Tuberculosis Epidemiologic Studies Consortium
IRB/IACUC#: 2018-014
Factors Affecting the Spatial-temporal Distribution of Tuberculosis in Texas - 2012-2016

1) Purpose

Tuberculosis (TB) is a chronic disease that mostly affects the respiratory system. It is among the top 10 causes of death worldwide, according to the World Health Organization (WHO), even though a preventable disease. In Texas, data from the Texas Department of State Health Services (DSHS) reveals that TB remains a relatively significant disease. Several risk factors have been linked to a predisposition of TB infection. Such risk factors include HIV/AIDS and other immunodeficiency states (e.g. diabetes), alcohol abuse, poverty, etc. The objective of this study is to determine the geographical distribution of TB in Texas and to assess how HIV/AIDS prevalence and median household income correlate with the spatial pattern of TB in the state.

2) Methodology

TB prevalence rates for the years 2012-2016 were obtained for all counties in Texas from the Texas Department of State Health Services (DSHS) while prevalence rates for HIV/AIDS were obtained from Texas Ranking Data. Median household income was used as an indicator of SES; the data was obtained from Texas Ranking Data. Temporal-spatial variations in TB and HIV/AIDS prevalence were analyzed using ArcGIS. Multiple linear regression models were used to regress TB prevalence on HIV/AIDS and median household income.

3) Results

TB prevalence in the state has been relatively low in the last five years at about a mean of 4.5 per 100,000. Counties in the south of the state have had the highest burden of the disease. HIV/AIDS prevalence was found to be positively correlated with TB prevalence, adjusting for demographic factors.

3) Conclusion

Even though the average TB prevalence in the state is low, preventive measures should still be promoted, especially among vulnerable populations, to maintain the low rates. HIV/AIDS prevention efforts should also be intensified because a successful HIV/AIDS program (resulting in low prevalence rates) will ultimately lower TB prevalence.

Sponsor: N/A
IRB/IACUC#: N/A
Differences by Depression Severity Category in Cigarette Smoking Among Low-Income Housing Residents

Purpose: Smoking is especially prevalent in low-income groups with additional characteristics. Smoking prevalence is estimated to be 70% among homeless individuals and 77% among low-income substance users in treatment. Among the low-income and mentally ill, the smoking prevalence is 31.7%. The most common mental illness, depression, has been frequently studied as a comorbidity of smoking. Approximately 60% of individuals with depression are current or former smokers. This association has often been studied with a binary measure of depression, which may overlook the effects of depression severity on smoking behavior.

Methods: This study used data collected from participants in subsidized housing enrolled in a health coaching intervention called “Mobile Community Health Assistance for Tenants” or “m.chat.” The sample included 420 residents with a mental health condition. A zero-inflated Poisson regression was used to determine the association between smoking cigarettes and four levels of depression: minimal or none (PHQ9 ≤4), mild (PHQ9 5 - 9), moderate (PHQ9 10 - 14), and severe (PHQ9 ≥15).

Results: The majority (73.3%) of individuals smoked an average of 7.5 cigarettes per day. In our population with a high prevalence of smoking and depression, when we controlled for depression severity, we found that those without depressive symptoms were more likely to smoke. Depression risk was significantly associated with both the likelihood of smoking (chi-sq=11.03, p=0.0116) and the number of cigarettes smoked among smokers (chi-sq=14.89, p=0.0019). Moderate depression severity resulted in increased odds of being a smoker (OR=2.16, 95%CI:[1.01,4.64]), but a decrease in the number of cigarettes smoked (RR=0.87, 95%CI:[0.77,0.99]).

Conclusion: Further study is warranted to examine the relationship between depression severity and cigarette smoking.

Sponsor: N/A
IRB/IACUC#: 2014-125

Purpose: Preventable medical errors are the third leading cause of death in the United States annually. The Healthcare-Acquired Infections (HAI) Prevalence Survey estimated 722,000 HAIs occurred across all United States acute care hospitals in 2011, with nearly 10% mortality. Previous studies demonstrate that proper hand hygiene (HH) practices significantly reduce the incidence of HAIs. The present study aims to assess HH practices at John Peter Smith (JPS) Hospital through a mixed top-down and bottom-up approach.

Methods: For the top-down assessment, UNT/HSC students acted as secret observers recording employee compliance with the World Health Organization’s 1st & 5th moments of Hand Hygiene. These observations were performed on 2 Scope Units at the JPS Hospital. Phase 1 identified areas of low HH compliance based on time and date, with 3,461 opportunities observed. Phase 2 included data on HH compliance by roles as well (e.g. nurse, physician/PA, tech/MA, EVS, family), with 1,362 opportunities observed. For the bottom-up assessment, 71 employees on the observed units were surveyed to gain targeted feedback about their education in HH, compliance, culture, and ideas for improving HH in the workplace.

Results: The Secret Observer Recordings found 41.3% overall compliance with HH protocols. The areas with most opportunity for improvement are: before entering the patient room (36.2% compliance), individual role (physician: 20.3%, and family member: 2.3%), certain days of the week (Sun, Wed, Fri) and times of the day (10:00–17:00, and 17:00–22:00). The post-observation survey noted that the top 4 reasons for not practicing HH were being in a hurry, lack of training/knowledge, forgetfulness, and lack of hand sanitizers/sinks.

Conclusion: Identifying areas with the greatest potential for improvement will allow strategic policy development to enhance future HH compliance. Taking measures to ensure JPS personnel feel comfortable to telling others to “wash their hands” will further solidify behavioral changes. This
comprehensive approach will foster a unique culture of safety that reduces the spread of HAIs, significantly improving quality of patient care patients.

Sponsor: N/A

IRB/IACUC#: JPS-050216.004ex
Does the Relationship Between Depression and Physical Activity Differ by Gender in Young Adults Ages 25-34?

Purpose: Depression has become a significant health concern in the United States and has been linked to physical activity in previous research; however, there is insufficient research on the relationship between physical activity and depression between genders in young adults ages 25-34. The purpose of this study was to determine whether the relationship between physical activity and depression differs by gender in young adults ages 25-34.

Methods: This cross-sectional analysis used 2015 data from the Behavioral Risk Factor Surveillance System (BRFSS) for males and females ages 25-34 from Maine, Oregon, Rhode Island, and Vermont. Multiple logistic regression analysis was used to assess the relationship between depression and physical activity, while controlling for age, ethnicity/race, income level, weight status, tobacco use, alcohol use, and activity limitations.

Results: Across states, about one-fourth of young adults reported ever having been diagnosed with depression or dysthymia (25-29%) or being highly active (22-36%). After controlling for demographic factors, socioeconomic status, and psychosocial factors, depression was not significantly related to physical activity in males or females in ME, OR, or VT. However, depression was significantly related to activity limitations in both males and females in all four states, and significantly related to tobacco use in females in ME, OR, and RI.

Conclusions: Overall, depression was not significantly related to physical activity in males or females ages 25-34. However, depression was significantly related to activity limitations in both males and females in all four states as well as tobacco use in females in three of the four states. This study was limited by an inability to obtain information on duration, extent, or prior treatment of depression in participants. Although the prevalence of depression may be low to moderate in primary care, it is recommended that providers screen all young adults for depression if they present with depressive symptoms and refer to a mental health clinic for treatment. Additionally, providers should screen all young adults with depression for activity limitations as well as young adult females with depression for tobacco use, and vice versa, and provide education, treatment, and referrals as needed.

Sponsor: N/A
IRB/IACUC#: 2017-070
Association Between Infant Breastfeeding and Early Childhood Caries in the United States

Purpose

Despite the limited epidemiologic evidence, there has been concern that breastfeeding and its duration may increase the risk of early childhood caries. The objective of the study is to determine if there is an association between breastfeeding and its duration and the risk of early childhood caries among young children in the United States.

Methods

Data from the 2011-2014 NHANES database, a cross-sectional survey conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention, were analyzed. Data consists of 1771 Children between age 2 and 5 years of age with information on both infant feeding and oral health. According to the guideline from American Academy of Pediatric Dentistry, early childhood caries (ECC) and severe early childhood caries (SECC) were defined as the presence of any decayed or filled surfaces (DFs) in primary tooth and the presence of DFs in any maxillary incisors in children, respectively. The association of breastfeeding and its duration, as well as other factors that previous research has found associated with early childhood caries, were examined in unconditional bivariate analyses and multivariable logistic regression analyses and presented with estimated odds ratios (ORs) and 95% confidence intervals (95% CI).

Results

The prevalence of ECC and SECC were 25% and 8% of the study population. After adjusting for potential confounders significant in bivariate analyses, breastfeeding and its duration was not significantly associated with the risk for early childhood caries (ever vs. never breastfed, OR:1.16, 95%CI: 0.65,2.05). Independent associations with increased risk for early childhood caries were older child age (age 4 vs. 2, OR: 4.62, 95%CI: 2.38, 8.97, p for trend200 vs.

Conclusions

Breastfeeding or its duration didn’t present an elevated risk of early childhood caries, severe early childhood caries on primary teeth among US children aged 2 to 5 years old. There was an association between family poverty status, race (Mexican American), birth weight, and early childhood caries. These findings can be used to design more robust early child dental health programs for Mexican Americans that live in poverty.

Sponsor: N/A
IRB/IACUC#: 2017-104
A comparison of treatment acceptance and adherence rates among two populations at high risk to develop tuberculosis in Tarrant County, Texas

Background: After decades of declining incidence rates, progress toward US tuberculosis (TB) elimination goals has begun to stall and perhaps even reverse. In light of this alarming trend, the strategic approach to TB control has begun to place more emphasis on carefully targeted surveillance for and treatment of latent TB infection (LTBI). Approximately 13 million people in the US have LTBI, and both LTBI and active TB are much more prevalent among homeless persons, refugees, and immigrants from high burden settings.

Without treatment, 5-10% of persons with LTBI will develop active TB during their lifetime, and most (>85%) US patients with recent incident TB have a prior history of LTBI. Still, LTBI is an asymptomatic condition that can be difficult to diagnose, and treatment acceptance and adherence are critical barriers to related prevention efforts. A 2012 report estimated that treatment acceptance and completion rates in the US were only 26% and 53%, respectively, and these vary widely by population. For instance, adherence is 7.2 times higher among the refugee population compared to the homeless population, however, the treatment completion rate is low for both.

Local public health departments (PHD) are ultimately responsible for the protection of their catchments through TB surveillance, outpatient treatment, and prevention activities. A complete understanding of how patient characteristics may influence treatment acceptance and adherence is critical to successfully implementing risk targeted TB control strategies at the local level.

Purpose: We analyzed acceptance and adherence for refugee and homeless patients offered treatment for diagnosed LTBI in Tarrant County Public Health’s TB and Refugee Clinic. Understanding factors associated with accepting and completing LTBI treatment in these high-risk populations inform public health action at the local level and contributes to individual and community health protections.

Methods: We examined LTBI treatment acceptance and adherence among homeless and refugee research subjects in an urban public health clinic in Tarrant County, Texas during January 2013 to December 2016. Our retrospective analysis used deidentified local data collected as part of a larger project by the CDC’s Tuberculosis Epidemiologic Studies Consortium. We used multiple logistic regression and chi-square to compare outcomes while controlling for demographic, clinical, and other factors.

Results: To be calculated.

Conclusions: Will be complete soon.

Sponsor: N/A
IRB/IACUC#: 2018-014
Health disparities in age of first concern and age of diagnosis for children with ASD, ADHD, and ASD+ADHD are evident in a national sample

Background: Autism Spectrum Disorder (ASD) is diagnosed in 1 out of 68 children. Individuals with ASD commonly meet criteria for comorbid conditions such as Attention Deficit-Hyperactivity Disorder (ADHD). Although previous diagnostic guidelines (DSM-IV) did not permit clinicians to assign co-occurring diagnoses of ASD+ADHD, this became allowable in 2013 (DSM-V). Due to this change and a high prevalence of ASD+ADHD, it is important for researchers and clinicians to be aware of groups vulnerable to delayed or incomplete diagnosis.

Objective: Assess the impact of race, ethnicity, sex, poverty level, and diagnosing provider type on age of first concern and age of final diagnosis in children diagnosed with Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and ASD+ADHD.

Hypothesis: We predicted that age of first concern would vary by sex, race, poverty level, identifier of first symptoms, and comorbidities. We also predicted that age of final diagnosis would vary by sex, race, poverty level, identifier of first symptoms, and provider type.

Method: Data were extracted from the CDC Survey of Pathways to Diagnostics and Services (SPDS) and the National Survey of the Diagnosis and Treatment of ADHD and Tourette Syndrome (DTAT). Parents/guardians of 5,959 children aged 3-17 completed the surveys; in the current sample, 2,966 cases were from DTAT and 2,993 were from SPDS. The datasets were recoded and merged for analysis. We used a series of ANOVAs to assess differences in the variables of interest, grouped by demographics (sex, race, poverty level), identifier of first concerns, previous and current co-morbid conditions, and provider type.

Results: Age of first concern was significantly impacted (p < 0.05) by Race, Race x Poverty Level, and Race x Poverty Level x Sex for the ASD+ADHD group. Age of final diagnosis was significantly impacted (p < 0.05) by Poverty Level, Race x Poverty Level, and Sex x Race x Poverty Level for the ASD group. Identifier of first symptoms significantly impacted (p < 0.05) age of first concern for all groups, while identifier of first concerns only significantly impacted (p < 0.05) the ASD and ADHD groups. Post-hoc analyses revealed specific patterns of risk.

Conclusion: Specific combinations of demographic factors increase vulnerability for later diagnosis. These findings suggest that provider- and patient-centered education is needed to increase surveillance in at-risk populations.

Sponsor: N/A
IRB/IACUC#: 2017-138
Comparison of Pulmonary Impairment after Tuberculosis in patients treated with Moxifloxacin-based regimens vs standard RIPE (Rifampin-Isoniazid-Pyrazinamide-Ethambutol)

Purpose: Tuberculosis (TB) is a global health-care problem. Of the 9.6 million people affected every year, 1.6 million die, and 70% of remaining survivors develop functional and anatomical lung damage. The lung injury after cured TB has been well characterized and is known as Pulmonary Impairment after Tuberculosis (PIAT). PIAT occurs despite completion of treatment with standard RIPE (Rifampin, Isoniazid, Pyrazinamide, and Ethambutol) regimen. Moxifloxacin regimens have shown effectiveness curing PTB besides having an immuno-modulatory effect that may limit extension and severity of tissue destruction in the lung.

Hypothesis: Patients receiving Moxifloxacin based regimen for PTB exhibit less frequent and reduced severity of PIAT in comparison with those receiving standard regimen (RIPE).

Methods: We compared results of Pulmonary Function Test (PFT) in 166 patients diagnosed with PTB. Twenty-three were treated with a Moxifloxacin-based regimen (sponsored clinical trial) and 143 with standard regimen (RIPE). Pulmonary impairment (presence and severity) was assessed following AMA criteria. FVC, FEV1, and FEV1/FVC ratio values were compared with predicted values considering gender and race standards. Lung restrictive defect was defined as FEV1/FVC ratio >70% with an FVC < 80% of predicted. Airway obstruction was defined as FEV1/FVC ratio80% of predicted. Mixed pattern was FVC of < 80% predicted and FEV1/FVC ratio 20 weeks of therapy when culture results were negative. Demographic and risk factors for lung impairment were collected.

Results: Both groups had similar risk factors for lung impairment. PIAT was present in 35% of patients receiving Moxifloxacin and 57% of patients receiving standard RIPE regimen (p =0.0510). Mean FVC, FEV1, FEV1/FVC ratios flow, and FEF 25-75 values showed no significant difference between the two groups. Patients treated with RIPE regimen showed predominately restrictive pattern of disease compared with those in Moxifloxacin. Twelve patients treated with standard RIPE regimen had 50% less of their expected vital capacity vs none in the group treated with Moxifloxacin. After adjusting for other risks associated with lung impairment and severity, we found that patients receiving standard RIPE regimen had 2.5 more risk of having abnormal PFT in comparison with patients in Moxifloxacin (95% CI (1.03-6.18).

Conclusion: These data confirm our previous findings of residual lung impairment in near half of patients cured of PTB. Patients treated with Moxifloxacin regimen had less impairment than those who received standard regimen. Restrictive pattern of disease was predominant in patients treated with standard regimen. Further research is required to assess the effect of Moxifloxacin on PIAT.

Sponsor: N/A
IRB/IACUC#: 2017-099
Pick a Card: An Autonomy-Building Exercise to Promote Healthy Lifestyle Behaviors

Purpose:
Providing options can be beneficial to participant success by promoting a greater sense of autonomy about individual changes which promote health. Developed with the goal to guide participants of a social-network based women’s wellness intervention, health behavior cards were created using health and wellness evidence-based information. The purpose of this research was to develop a tool to allow program participants the flexibility and autonomy to make choices regarding individual behavior changes.

Methods:
Using evidence-based literature, health behaviors were chosen to align within the 5 domains guiding SHE Tribe (Me, Mind, Mater, Move, and Meet). For each behavior, evidence in the literature was found supporting the effectiveness to improve health. The behavior and evidence were then incorporated on the card, for example, “Skip the salt and try adding spices, herbs, and seasonings to your food. Less sodium (salt) can help lower your risk for high blood pressure.” This tool provides participants choices for their health behaviors, but also a rationale for why it would be beneficial to consider adopting.

Results:
This process resulted in the creation of a 54-card deck of health behavior changes. Through participation in SHE Tribe, participants will receive the cards with the objective of to prompt participants’ reflection and goal-setting as they go through the program. The cards can also be used after the program has ended.

After the first gathering, participants receive custom feedback with scores associated in each of the 5 domains. In addition to the feedback, the cards will allow participants to tailor the program to their needs. Used as a way to identify small yet achievable changes toward a healthier lifestyle, the cards can be used in 2 ways. Whether guided by a facilitator to help participants reflect on their health and identify potential health changes through discussion, or used individually, the cards will serve as a tool to continue exploring small, but positive, health behaviors.

Conclusion:
Having choices is necessary to strengthen motivation and empowers program participants to make their own meaningful health changes. A deck of cards that includes 54 empirically-supported health behaviors supports individuals’ capacity to select behaviors that best meet their needs and lifestyle. By setting goals with the use of the cards, self-efficacy is increased making changes to health behaviors more likely to be achieved.
Sponsor: N/A
IRB/IACUC#: 2017-148
Assessment of Variability in Intent to Vaccinate against HPV among Caregivers of Pediatric Patients

Purpose: HPV is the leading STD in the United States and the primary cause of cervical cancer in women worldwide. The HPV vaccine has a high success rate in protecting against high-risk strains of HPV, however vaccination rates are low. The purpose of this study is to identify barriers to vaccination administration by focusing on racial disparities when factoring income, education, and provider recommendation for the vaccine as effect modifiers.

Methods: Multiple choice surveys were given to the parents/guardians of pediatric patients of the department of Pediatrics that consisted of 50 questions regarding the patient’s socioeconomic status and knowledge/opinions of HPV and the vaccine. A five to ten-minute education session was given after the encounter and a handout about HPV and the vaccine was given to parent/guardian to take home. Ordinal logistic regression was performed in order to obtain results.

Results: Ordinal Regression showed that parents with some higher education, incomes between 40,000-70,000 a year, and who are Non-Hispanic whites had decreased intent to vaccinate their children.

Discussion: The study focused on obtaining factors such as income, education, and race as effect modifiers in relation to the intent to vaccinate. Race was the most influential factor, and Non-Hispanic Caucasians appeared to be less likely to vaccinate than Hispanic populations, contrary to multiple studies. Secondly, lower levels of education did not correlate with less intent to vaccinate. Those with some higher education were less likely to want to vaccinate their children, while those with high school or below had more intent. Lastly, the more income an individual had, the less likely they were willing to vaccinate. All findings were contrary to the hypothesis that Hispanic populations, lower income, and lower education levels would have less intent to vaccinate. Some factors in the study did not have enough data to compute a substantiated analysis. Suggestions for further research would be to collect more surveys from missing demographics and clarification of questions to avoid confusion about intent to vaccinate. Barriers were finding subjects with children in target age groups.

Conclusion: Race, income, and education did have an effect on whether a parent had intent to vaccinate their child with the HPV vaccine. However, the results showed that those who were Non-Hispanic Caucasians, higher income, and obtained some higher education were less likely to want to vaccinate their children in comparison to other populations. Multiple studies showed that minorities and lower income populations were less likely to get the vaccine series due to lack of knowledge and less provider recommendation, though they do not investigate the intention to vaccinate. Provider recommendation seemed to be the most influential factor in increasing vaccination rates in these studies. This project is a living study and will be edited to provide more target questions for certain demographics and clarify questions that surveyors had difficulty answering.
Sponsor: N/A
IRB/IACUC#: IRB #2015-148
Does Alcohol Misuse Differ by Gender and Veteran Status in Adults Ages 25 and Older?

Purpose: There are conflicting findings across previous studies regarding prevalence of alcohol use, binge drinking, and heavy drinking between veteran males and females, and compared to civilians. The purpose of this study was to assess whether alcohol misuse differs by gender and veteran status in adults 25 and older.

Methods: Data from the 2015 BRFSS for Maine, Montana, Oregon, South Carolina, and Alaska for veteran and non-veteran males and females ages 25 and older were used in this cross sectional analysis. Multiple logistic regression analysis was used to assess the relationship between alcohol misuse (use, binge, heavy) and veteran status by gender after controlling for age, education level, income level, marital status, race, depression, and smoking status.

Results: For adults ages 25 and older, about half (44-59%) reported alcohol use, and about one-tenth reported binge drinking (10-15%) or heavy drinking (5-7%) in the past 30 days. After controlling for demographic and lifestyle factors, alcohol use and binge drinking were directly related (small to moderate effect sizes) to gender and veteran status, with males, both veteran and non-veteran, showing more than female non-veterans in Maine, Montana, Oregon, South Carolina, and Alaska. There was no overall pattern across states for heavy drinking.

Conclusion: Overall, alcohol use, binge drinking, and heavy drinking were related to gender and veteran status. Binge drinking and heavy drinking were also related to smoking. For veteran and non-veteran adults ages 25 years and older in a primary care setting, a moderate prevalence of alcohol use may be expected, while a low prevalence of binge drinking, heavy drinking, and smoking may be expected. Although these prevalences may be low, standard of care is to automatically screen for alcohol use and smoking in all patients, both veteran and non-veteran. Therefore, in a primary care setting if signs of binge or heavy drinking are present, providers should consider a more in depth screen for alcohol misuse. Additionally, if signs of either alcohol misuse or smoking are present, providers should consider a more in depth screen for both. Patient education and referrals for alcohol misuse treatment programs and/or smoking cessation counseling should be provided to patients as needed.
Sex Differences in the Effect of Physical Activity on Teen Sleep Patterns

Introduction: Insufficient sleep durations, irregular sleep patterns, and poor sleep quality predict obesity including adverse changes to obesity-related outcomes like decreased physical activity (PA). In turn, increasing PA positively impacts sleep durations and quality. The transition from childhood to adolescence brings a decrease in PA with females showing a more significant decrease. This decrease in PA may be a contributing factor to the high rates of insufficient sleep and irregular sleep patterns in teens. To better understand these connections, we examined how PA influenced sleep duration and quality in teens. We expected that higher PA durations would predict longer sleep durations, more regular sleep patterns, and better sleep efficiency. We also explored sex differences to better understand how these connections play out during adolescence.

Methods: Current analyses utilized baseline data from the initial week of a larger project (PI: Roane) that examined sleep and obesity-related behaviors in teens. Teens and caregivers provided informed consent/assent. Teens were given activity monitors to continuously capture sleep and physical activity. After one week, height and weight were measured for BMI %tile calculation. Sleep duration, sleep efficiency (SE), and physical activity were calculated from retrieved activity monitor data. Regression analyses examined mean physical activity duration as a predictor with BMI %tile as a covariate for (a) mean sleep duration, (b) sleep duration variability, (c) mean sleep efficiency, and (d) sleep efficiency variability.

Results: Teens (n=26) were age 15 years, 27% Hispanic, 42% African American, and 73% female. Mean BMI %tile was 65th (female[f]: 71st, male[m]: 48th) and PA duration was 91 min (f: 82, m: 117). Mean sleep duration was 433 min (f: 429, m: 444); sleep duration variability was 78 min (f: 79, m: 74); SE was 95 (f: 95, m: 93); and SE variability was 5 (f: 5, m: 5). Regression analyses found PA duration predicted mean sleep duration. Analyses by sex indicated PA duration accounted for 74% of the variance in sleep duration for males only. All other findings were not statistically significant.

Conclusions: Our analysis showed higher PA predicted longer sleep duration in males. These data provide further support for sex driven differences in how sleep contributes to obesity. Further study with a larger sample is warranted to better understand sex differences in the connection between sleep and obesity.

Sponsor: PDRT
IRB/IACUC#: 2013-015
Mapping, Characterization and Description of HIV-APPE Rotations at ACPE Accredited Colleges of Pharmacy

Background: Despite aggressive HIV testing programs and the introduction of preventative antiretroviral regimens (PrEP), the number of persons living with HIV in the United States (US) continues to increase by over 30,000 every year. As over 50% of PLWH are now over the age of 50, they represent an especially challenging population to provide care as they develop co-morbid conditions consistent with their non-PLWH counterparts of the same age, gender, race and ethnicity. In order for healthcare teams to optimally care for this population, pharmacists with focused training in this disease state are required. Accredited colleges of pharmacy, federal training programs and other large healthcare systems must first be knowledgeable of where to send trainees, yet no comprehensive database of HIV-specialized pharmacist training sites currently exists.

Objective: This study's primary aims were to (1) create a map of US-based pharmacy student training sites, then describe (2) the training environment and (3) qualifications of the trainer present.

Methods/Materials: A forced-choice, logic, algorithm based, Qualtrics™ survey was developed, validated, IRB-approved and deployed using a four-pronged approach. From October to November 2017, this anonymous survey was distributed through (1) professional organizations membership lists (pharmacy and medicine, HIV and non-HIV focused), (2) ACPE accredited pharmacy schools' experiential coordinators, and (3) a nationwide pharmacy chain. The 4th prong was via grassroots, snowball distribution whereby recipients forwarded it to their contacts.

Results: Of 170 survey respondents, 143 consented to participate. Not all responded to each question. Results reflect proportion of question responses. Respondents reported 65% (n=94) primarily provide care for PLWH, 48% have at least 100 HIV patients served annually, and 79% (n=143) receive some form of government funding. Of the 143, 78 (59%) are APPE sites, 55 of which take over 6 students annually. Most students (93%) engaged 10 patients per week and 8 of 10 patients were PLWH. While 60 (42%) of these APPE sites report affiliation with at least 1 college of pharmacy, 18 states were not captured, including areas with high prevalence of PLWH.

Conclusion: The survey successfully identified predominantly high patient volume HIV training sites, with experienced preceptors in 32 states. Serial deployment with enhanced marketing is needed to identify the regions not represented.

Sponsor: N/A
IRB/IACUC#: 2017-098
Impact of a Randomized Church-based, Lifestyle Intervention on Allostatic Load in African American Women in Dallas

Purpose: African American women have higher rates of cardiovascular risk factors and greater than 50% higher mortality from cardiovascular disease than White women. This disparity may be explained by the uniquely higher allostatic load found in African American women. Allostatic load represents the physiologic cost to adapting to chronic and significant stressors throughout the life-course. Though poor nutrition and physical inactivity have shown inconsistent correlations with allostatic load in African American women, there have been no studies testing the effect of lifestyle interventions on allostatic load in this group. Our objectives are to (1) assess the change in allostatic load following a lifestyle intervention, (2) explore the role of health behavior changes and allostatic load, (3) evaluate how socioeconomic (SES) variables including neighborhood SES influence these relationships.

Methods: Study participants were non-diabetic (48.8±11.2y) AA women (n=221) randomized to a church-based, standard diabetes prevention program (DPP) or a faith-enhanced DPP. Allostatic Load (AL) score was calculated at baseline and 4-month follow-up using the high-risk quartile method of 9 biomarkers: systolic and diastolic blood pressure, total cholesterol to high-density lipoprotein (HDL) ratio, HDL, triglycerides, hemoglobin A1c, body mass index, salivary cortisol, and waist circumference. We assessed perceived stress, neighborhood disadvantage, individual SES, physical activity, and other lifestyle variables. Multinomial logistic regression model was used to estimate the effect of lifestyle factors, perceived stress, and neighborhood disadvantage on change in AL.

Results: AL was reduced (-0.12±0.99, p=0.04) from baseline to 4-month. 39% of participants had lower AL and 19.5% had increased AL. After adjusting for age and intervention effects, low level of education (high school degree or less) (OR:0.037, CI:0.004–0.379) and alcohol consumption (OR:0.091, CI:0.020–0.421) contributed to increased AL. Other variables were positively, but not statistically associated, with decreased AL.

Conclusions: More research is necessary to determine the roles of perceived stress, physical activity, and weight loss in reducing AL. Lower education levels and alcohol consumption may dampen the effect of positive lifestyle behaviors in reducing AL.

Sponsor: PDRT: National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R25HL125447 (to Dr. J.K.Vishwanatha)

IRB/IACUC#: 2011-164
Does Alcohol Use Affect the Relationship Between Social Support and Depression? An Examination of Permanent Supportive Housing (PSH) Residents in Fort Worth, Texas

Background: Social support tends to be protective against depression in a wide variety of groups. However, relatively little is known about how alcohol use might affect this relationship over time, especially among supportive housing residents, who are at risk for both depression and poor social support.

Purpose: This study examined whether the association between social support and depression was modified by alcohol consumption among permanent supportive housing (PSH) residents in Fort Worth, Texas.

Methods: We used the baseline and 6-month follow-up data from the Mobile Community Health Assistance for Tenants (m.chat) program, collected during 2014-2017. m.chat was a technology-assisted health coaching program for people with mental health conditions residing in PSH in Fort Worth, Texas. Participants’ current levels of depression and social support were measured using Patient Health Questionnaire-9 (PHQ-9) and Interpersonal Support Evaluation List (ISEL), respectively; alcohol consumption was measured via a self-report frequency measure that ranged from “0” (never) to “4” (more than 4 times a week). The association between social support and depression was studied using generalized estimating equation (GEE) models including alcohol use as an effect modifier and sex, age, race, marital status and perceived physical health as a priori covariates. This analysis included 567 participants.

Results: At baseline, about 38.2% of participants reported some alcohol consumption in the past 90 days. Greater baseline social support was associated with improvements in depression severity. One unit increase in the baseline ISEL score predicted a 4.3% reduction (95%CI: 2.6%, 6.1%) in depression scores over time. Greater baseline alcohol consumption predicted an 11.9% increase (95%CI: 0.8%, 21.6%) in depression scores over time. We did not find a significant interaction between alcohol consumption and social support and changes in depression severity after adjusting for sex, age, race, marital status and perceived physical health.

Conclusions: Among PSH residents in Fort Worth, Texas, greater social support was associated with a reduction in depression scores. Higher alcohol consumption was associated with an increase in depression scores. The protective effect of social support did not differ by alcohol consumption level. These findings can be used to design more robust health coaching programs for formerly homeless persons that integrate positive social support.

Sponsor: N/A
IRB/IACUC#: 2017-157
Immunology (Abstracts in the 1300s)

1300 - Poster

**Classification:** GSBS Student

**Presenter:** Rudy Castillo

**Department:** Physiology and Anatomy

**Authors:** Rudy Castillo, University of North Texas Health Science Center at Fort Worth; Lisa M Hodge, Ph.D., Department of Physiology and Anatomy

**Lymphatic pump technique mobilizes lymph that inhibits the inflammatory response of macrophages in vitro**

Purpose: The lymphatic system maintains tissue fluid homeostasis by returning excess fluid, known as lymph, into circulation. Osteopathic physicians recognize the importance of the lymphatic system and have designed a set of lymphatic pump techniques (LPT) that enhance the flow of lymph. LPT has been used clinically to treat respiratory tract disease, infection, and edema. LPT has also been reported to enhance mesenteric and thoracic lymphatic flow, the concentration of leukocytes, and the flux of inflammatory mediators in lymph of dogs. We propose LPT may act as an adjunctive therapy by mobilizing lymph-borne factors into circulation that protect tissues during inflammation. In this study, we propose that lymph mobilized by LPT suppresses macrophage activation *in vitro*.

Methods: To test this hypothesis, under anesthesia, the thoracic ducts of six mongrel dogs were cannulated and thoracic duct lymph (TDL) was collected before (baseline), during, and after (recovery) LPT. TDL supernatant was collected by centrifugation and frozen. Total protein was measured in TDL using the Bradford method. Murine RAW 264.7 macrophages were cultured with baseline, LPT, or recovery TDL at 5% total volume per well with or without lipopolysaccharide (LPS) for 24 hours at 37°C and 5% CO₂. After culture, cell-free supernatants were assayed for nitrite (NO₂⁻), tumor necrosis factor-alpha (TNF-alpha), and interleukin-10 (IL-10). Macrophage viability was measured using flow cytometry and markers, annexin V and propidium iodide.

Results: LPT transiently increased TDL flow and protein flux (10-fold). Baseline, LPT, or recovery TDL did not increase the production of NO₂⁻, TNF-alpha, IL-10 or alter macrophage viability. When macrophages were activated with LPS, the addition of baseline, LPT, or recovery TDL decreased the production of NO₂⁻ (2-fold), TNF-alpha (5-fold) and IL-10 (3-fold) compared to LPS. There were no significant (p>0.05) differences in the production of NO₂⁻, TNF-alpha, and IL-10 by macrophages cultured with baseline, LPT, or recovery TDL and LPS.

Conclusions: Our data suggests that lymph contains biological factor(s) that suppress macrophage activation without altering cell viability. The redistribution of protective lymph during LPT may provide scientific rationale for the clinical use of LPT to treat inflammation and edema. Future studies will focus on the mechanism(s) responsible for these novel findings.

**Sponsor:** NIH R01AT004361

**IRB/IACUC#:** IACUC 2007/08-37
Atrophied thymus produces altered repertoire of tTregs with potential to break the balance of peripheral tolerance

Purpose: We have previously shown that in the age-related atrophied thymus, there is an increased ratio of thymic T regulatory (tTreg) cells to thymic T conventional (tTcon) cells, suggesting that the aged thymus has an enhanced tTreg generation. It is also known that in the periphery of aged mice and humans, there is an accumulation of peripheral Tregs. We raise the following question: why is the increased Treg population unable to suppress self-reactivity in the elderly?

Methods: We utilized a sub-lethally irradiated chimeric mouse model in which OT-II TCR transgenic bone-marrow cells were transplanted into RIP-mOVA host mice. Therefore, OVA serves as a mock self-antigen, and because this transgene is driven by the rat insulin promotor, the pancreas of these mice expresses OVA. Further, the mOVA mice also carry a FoxN1-floxed gene, which can be conditionally knocked-out via CreER\(^{T}\) transgene activation by injection(s) with tamoxifen to induce thymic atrophy.

Results: We observed that chimera mice with induced thymic atrophy show total Tregs (termed pan-Tregs) were increased but OT-II specific Tregs were slightly decreased in the spleen. Additionally, there is a dramatic decrease in the OTII-specific Tregs found in the pancreas, and pancreatic atrophy was observed in these mice compared to those with normal thymus.

Conclusions: Our initial results suggest that thymic atrophy leads to a biased tTreg generation that manifests in decreased self-tissue specific-Tregs. Therefore, although pan-Tregs may accumulate and be enhanced with age, tissue-specific peripheral tolerance may be poised to fail.

Sponsor: NIH/NIAID 1R01AI121147
IRB/IACUC#: 2016-0037
Free access to lard, sucrose, and chow results in expansion of rat periuterine adipose tissue.

Purpose: Adipose tissue expansion, a common feature of obesity, is associated with metabolic dysfunction, endocrine dysregulation, and adipokine imbalance. Adipocyte hypertrophy and hyperplasia contribute to adipose tissue expansion in a depot-specific manner. Our objective was to determine whether a high-fat, high-carbohydrate diet induces expansion of periuterine adipose tissue (PUT: adipose tissue surrounding the uterus). We hypothesized that free access to lard, sucrose, and chow results in hypertrophy and hyperplasia of adipocytes from rat PUT.

Methods: Sixteen Sprague-Dawley female rats were divided into 2 weight-matched groups (n=8 rats/group) after 5 days of baseline measurements of food intake and body weight. One group was offered free access to chow, 30% sucrose solution, and lard (choice group) and the other group remained on chow (chow group) for 3 weeks. Energy intake and body weight were recorded daily. After euthanization, PUT was collected, weighed, and fixed in 4% paraformaldehyde. Samples were embedded in paraffin, sliced into 5 μm sections, and stained with hematoxylin and eosin. To determine hypertrophy, hyperplasia, and cell morphology, we used NIS Elements software to measure cross-sectional area/cell, number of cells/unit area, and adipocyte size distribution, respectively.

Results: Total energy intake was greater in choice rats than chow rats (1590 ± 40.60 kcal/21 days vs. 1036 ± 19.00 kcal/21 days, p2/cell vs. 492.0 ± 27.76 μm²/cell, p=0.0001). The number of cells/unit area was smaller in PUT from choice rats compared to chow rats (13.9 x 10⁻⁵ ± 0.880 x 10⁻⁵ cells/μm² vs. 20.4 x 10⁻⁵ ±0.910 x 10⁻⁵ cells/μm², p=0.0001). PUT from choice rats had large adipocytes in greater frequency compared to PUT from chow rats.

Conclusion: Obesity induced by free access to chow, lard, and sucrose resulted in hyperplasia and hypertrophy of adipocytes, and in cell size distribution changes in PUT of female rats of breeding age. Future studies will investigate if obesity-induced PUT expansion influences reproductive capacity and gestational outcomes.

Sponsor: Styliani Goulopoulou
IRB/IACUC#: IACUC-2017-0042
High Salt Loading Increases Brain Derived Neurotrophic Factor in Supraoptic Vasopressin Neurons

Purpose: Salt loading (SL) upregulates Brain Derived Neurotrophic Factor (BDNF) and causes increased arginine vasopressin (AVP) release from supraoptic nucleus of the hypothalamus (SON). BDNF diminishes or reverses the GABA<sub>a</sub> inhibition in the SON AVP neurons by increasing intracellular chloride ([Cl<sup>−</sup>]) through tyrosine receptor kinase B (TrKB) phosphorylation. This creates a feed forward loop that drives AVP release. However, the source of BDNF is not known.

Hypothesis: We hypothesize that SON is the source of BDNF contributing to increased AVP release in SL rats.

Methods: Adult male Sprague Dawley rats were anesthetized with isoflurane (2-3%) and bilaterally injected in the SON (300 nl/side) with an AAV2 vector with a U6 promoter containing either shRNA against BDNF or a control construct with an mCherry reporter. The vectors were injected at a titer of 1.0 X 10<sup>13</sup> GC/ml (Vector Biolabs). Two weeks after the stereotaxic injections, the rats were provided with either water or 2%NaCl to drink for 7 days. At the end of the protocol, rats were anesthetized with inactin (100 mg/kg IP) and brains were collected and flash frozen. Fresh frozen brains were prepared for Laser Capture Microdissection (LCM) by cutting 10μm thick coronal sections through the hypothalamus at the level of the SON. Using LCM, we verified the accuracy of the injections by visualizing the mCherry reporter and collected the SON to measure changes in the BDNF mRNA and AVP hnRNA expression using quantitative Real Time PCR. Subset of brains from each group were used for Western blot analysis of punch samples containing the SON. Rats that did not have successful virus injections in the SON were separately analyzed. Plasma osmolality, hematocrit, and AVP concentration were measured. Data were analyzed by one-way ANOVA with Bonferroni comparisons.

Results: SL was associated with significant increases in BDNF mRNA and AVP hnRNA in SON (P

Conclusion: The results indicate that BDNF produced in the SON contributes to increased AVP secretion during SL.

Sponsor: R01 HL119458
IRB/IACUC#: 2014/15-29
Hypertensive young adult female obese zucker rats (OZR) do not have the blunted baroreflexes and poor glycemic control observed in age-matched hypertensive male OZR

Purpose: Obese Zucker rats (OZR) have hyperphagia owing to dysfunctional leptin receptors and gain excess weight compared to lean Zucker rats (LZR) with functional leptin receptors. Young adult male OZR (12-14 wks) develop hypertension and impaired baroreflexes coincident with blunted activation of the nucleus tractus solitarius (NTS), the brain stem site that receives baroreceptor afferent inputs. Male OZR at this age have hyperinsulinemia and chronically elevated fed glucose levels (despite normal fasting glucose) with significant glucose intolerance as measured by telemetry (DSI). Treatment with metformin (300mg/day, 4 wks) restores glycemic control in OZR without eliminating hypertension or hyperinsulinemia, with no effect on these measures in LZR. After treatment with metformin male OZR have improved baroreflexes and activation of the NTS, suggesting hyperglycemia contributes to these deficits in adult male OZR. In contrast to males, at this age female OZR are hypertensive but do not develop impaired baroreflex-mediated changes in heart rate (HR; Tenorio et al., 2013). The present study examined whether preserved baroreflex-mediated changes in HR in female OZR extend to sympathetic baroreflexes and diminished activation of the NTS and whether female OZR maintain glycemic control at this age (13-14 wks).

Method: Female zucker rats were instrumented with indwelling femoral catheters run through a tether to record MAP and HR and infuse drugs while rats were conscious and undisturbed. After 24 hours of rest, baseline parameters were recorded, and phenylephrine (PE) was infused through the venous line to raise MAP by 40 mmHg to evoke bradycardia response. PE infusion was continued for 90 min to evoke PE-induced c-Fos expression in the brainstem. A different set of rats was anesthetized with isoflurane for surgical preparation to measure MAP (femoral artery) and splanchnic sympathetic nerve activity (SNA) and to infuse drugs (femoral vein). Following this, the rat was anesthetized with urethane (1.5g/kg iv LZR body weight), ventilated, and paralyzed. Additionally, a set of female rats was instrumented with telemetry to monitor continuous glucose recording in undisturbed female zucker rats.

Results: Female OZR had excess weight gain (215±8 g vs. 483±14 g in 9 LZR and 10 OZR, P

Conclusion: These data suggest better maintenance of glycemic control in hypertensive, hyperinsulinemic young adult female OZR may preserve activation of the NTS and baroreflexes. In addition, these data highlight differing mechanisms for the development of hypertension and impaired control of SNA and HR by baroreflexes in the setting of metabolic syndrome.

Sponsor: NIHRO1HL138109, AHA GRNT18880005 to AMS, PRE27260088 to PC
IRB/IACUC#: IACUC-2017-0003
Sex-related Effects on Treatment Success in Obstructive Sleep Apnea

Purpose: Obstructive Sleep Apnea (OSA) has a high prevalence in adults in the US (over 20 million estimated diagnoses) for which the current gold standard treatment for OSA is Positive Airway Pressure (PAP). Current literature suggests a much higher occurrence in men than women and there appear to be sex-related disparities for treatment compliance as well. Current standards for treatment adequacy only require 4 hours/night and 5 days/week. We have developed a more rigorous Treatment Success Index (TSI) that combines key measures of PAP patient compliance and treatment efficacy. The purpose of this study was to determine whether there is a gender difference in TSI and, if so, what factors appear to contribute to these differences.

Methods: Retrospective analyses of sleep data from 150 patients were performed (#2018-019) to assess sex-related differences in TSI and determine how several treatment parameters and demographic factors affect the TSI.

Results: The findings revealed three main points. First, length of treatment versus TSI was significant for the males (P = 0.0307) but not the females (P = 0.0760). Second, age versus TSI was not significant for either gender (P > 0.05). Third, BMI versus TSI was significant for females (P = 0.0031) but not males (P = 0.1182). This suggests a longer treatment time in males and a higher baseline BMI in females are significant predictors of treatment success.

Conclusions: These data further define sex-related distinctions in the treatment efficacy of OSA and should be considered when physicians consider the management of their patients with OSA. Further studies will focus on the effects these factors might have on clinical outcomes.

Sponsor: N/A
IRB/IACUC#: 2018-019
Optimizing Treatment Success in Sleep Apnea

Purpose: Obstructive Sleep Apnea (OSA) is an exceedingly common disorder in America with estimates of disease prevalence ranging from 3-7% of the entire population, and it is likely that this is a gross underestimation. OSA is considered a multifactorial disorder with a diverse range of influences including developmental, environmental, and genetic factors. The current gold standard of treatment is Positive Airway Pressure (PAP). PAP treatment, while proven to be effective, is heavily influenced by many patient features. As a result, treatment success of OSA is difficult to predict and current standards do not take all the critical factors into account. The purpose of this study was to determine which patient traits can be used to predict treatment success.

Methods: We performed a retrospective analysis (IRB #2018-019) of de-identified patient data from sleep studies in 150 patients over time to calculate a newly developed Treatment Success Index (TSI). TSI is a novel measure that comprehensively measures patient treatment success by combining Apnea Hypopnea Index derived from the sleep data (AHI, a clinical measurement of disease severity) and specific measures of patient PAP compliance. We performed predictive statistical analyses to determine how several different parameters affected the calculated TSI.

Results: A linear regression was performed between BMI and TSI, which revealed a significant increase in treatment success secondary to increasing patient BMI (p=0.00002). In addition, patients were divided into three groups based on their length of treatment (LoTx), and a linear regression between the group average LoTx’s and their respective TSI’s revealed significant results (p=0.003).

Conclusions: These findings present new insights into factors that best predict treatment efficacy for OSA and may assist in optimizing patient treatment. Future studies will expand the scope of the utility of TSI as a new measure of treatment efficacy for OSA.

Sponsor: N/A
IRB/IACUC#: 2018-019
Immunological effects of vagus nerve stimulation in murine systemic lupus erythematosus

Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease that principally affects women and is associated with inflammatory pathogenesis of multiple organs. Of the disseminated features of SLE, classical disease processes such as renal injury with hypertension, as well as autonomic nervous system dysregulation, are prevalent. The autonomic dysfunction in SLE is characterized by increased sympathetic activity and concomitant decreased parasympathetic nervous system (PNS) activity; however, it is unknown if impaired PNS activity promotes hypertension and renal injury in SLE. The cholinergic anti-inflammatory pathway (CAP), is an endogenous neuroimmune reflex that regulates cytokine release from immune cells; briefly, the CAP initiates with stimulation of the parasympathetic vagus nerve and culminates in the inhibition of the secretion of pro-inflammatory cytokines from macrophages and other leukocytes. Although it is known that vagal activity is suppressed in SLE, it remains unclear whether this contributes to a diminished CAP promoting inflammation in the disease. We hypothesized that chronic vagus nerve stimulation (VNS) will decrease the inflammatory cascade in SLE through enhancement of the CAP.

Methods: Female SLE (NZBWF1) mice (25 weeks of age) were implanted with electrical vagus nerve stimulators that fit the cervical vagus nerve. Only female mice of this well-characterized strain were used, reflecting the prevalence of lupus in women. The mice were then divided into two groups: VNS (n=10) and sham (n=7). Stimulators targeted the vagus nerve continuously for 2 weeks.

Results: Spleen weight was slightly increased in SLE/VNS mice compared to SLE/sham mice (0.14 ± 0.03g vs. 0.11 ± 0.01; P=NS). Flow cytometry showed that SLE/VNS mice had slightly less CD3+/CD4+ bone marrow T cells when compared with SLE/sham mice (27.30 ± 9.41% vs. 40.17 ± 7.01%; P=NS). The percentage of mice with albuminuria, an index of renal injury measured by Albustix, was also decreased in SLE/VNS mice compared to SLE/sham mice (10% vs 29%).

Conclusions: These results suggest the efficacy of VNS in reducing the inflammatory profile in SLE mice, and that this protection may reduce end-organ disease. Future work will investigate the role of the CAP in quelling inflammation perpetuated by neuroimmune dysregulations in SLE.

Sponsor: Studies supported by the American Heart Association (14SDG18320033) and the National Institutes of Health (1K01HL139859)

IRB/IACUC#: IACUC-2017-0033
DREADD-induced inhibition of the MnPO affects drinking behavior and neuroendocrine function in adult male rats

Purpose: Angiotensin II (Ang II) is a peptide hormone that contributes to body fluid balance and hypertension. Forebrain circumventricular organs (CVOs) are sensitive to circulating Ang II and project to the median preoptic nucleus (MnPO). The MnPO projects to the paraventricular nucleus (PVN) and contributes to elevated sympathetic tone and thirst.

Methods: We used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to test the role of the MnPO in thirst and neuroendocrine responses to Ang II in adult male Sprague-Dawley rats (250-300g). Rats were anesthetized with isoflurane and stereotaxically injected with an inhibitory (Gi) DREADD (rAAV5-CaMKIIa-hM4D(Gi)-mCherry) or control (rAAV5-CaMKIIa-mCherry) virus in the MnPO. After 2 weeks of recovery, each rat was administered 10 mg/kg of exogenous Clozapine-N-Oxide (CNO) ip to inhibit DREADD expressing cells or vehicle ip followed by 2 mg/kg Ang II sc twice per week for 4 weeks. Rats were anesthetized with inactin (10 mg/kg ip) and transcardially perfused 90 minutes after CNO and Ang II treatments. Brains were processed for cFos and mCherry immunohistochemistry.

Results: DREADD-injected rats treated with CNO during Ang II exposure had a significantly attenuated drinking response compared to vehicle treatments or to control virus injected rats treated with CNO and Ang II (in vitro loose-cell voltage clamp recordings from DREADD-transfected MnPO slices indicated focal CNO (10 uM) application significantly reduces firing rates of these neurons. In situ hybridization experiments of DREADD-transfected MnPO neurons and vesicular glutamate transporter 2 indicated neurons transfected with the DREADD virus containing the CaMKIIa promotor are largely glutamatergic (89.17+1.32%).

Conclusion: The results indicate CNO-induced inhibition of excitatory, CaMKIIa-expressing MnPO neurons influences drinking behavior and neuroendocrine function.

Sponsor: Supported by NIH P01 HL088052 (JTC) and T32 AG020494 (ABM)
IRB/IACUC#: 2014/05-28-805
Oxazolone as a Model to Induce Edema in the Lower Limb of Rats

Purpose: Peripheral edema is a condition characterized by the accumulation of excess interstitial fluid in distal tissues and commonly manifests in the arms or legs. Untreated complex peripheral edema can progress into chronic lymphedema as impaired fluid drainage and chronic inflammation cause irreversible damage to the surrounding tissue and local lymphatics. The overall goal of our research is to study the effectiveness of osteopathic manipulative medicine treatments on edema, infection and inflammation. The aim of this research was to evaluate the oxazolone (OXA)-induced acute skin inflammation model to induce lower limb edema in the rat. Specifically, we hypothesized that the application of OXA would induce a local inflammatory response, induce edema in the lower limbs and decrease lymphatic vessel function.

Methods: Female Sprague Dawley rats, weighing 200-250 g, were used for this study. To induce edema, on day zero the right lower limb was shaved and 750 µl of 5% OXA-acetone solution or 5% PBS-acetone solution vehicle (VEH) was applied to the exposed skin. Lower limb measurements were made at days zero and six using a Vernier caliper. Measurements were taken at the midpoints of the hind paw, ankle, tibia and femur of their right lower limbs to establish paw thickness; distance between paw-to-ankle and ankle-to-tibia were taken to calculate lower limb volume by truncated cone formula. At day six, the rats were euthanized, and the bilateral hind paws were removed above the calcaneus and weighed. The spleen and bilateral inguinal lymph nodes were removed, homogenized, centrifuged and cells were washed. Cell pellets were stained with PE mouse anti-rat granulocytes, FITC anti-rat CD3, and APC anti-rat CD161 antibodies. The percentage of granulocytes, T cells and dendritic cells were measured by flow cytometry. Data were analyzed by ANOVA followed a Tukey post-test. Comparisons were made between OXA and VEH groups at day six post-induction.

Results: OXA did not induce significant (p>0.05) changes in either hind paw thickness or lower limb volume. OXA significantly increased...

Conclusions: OXA induced an acute inflammatory response in the draining inguinal lymph nodes. However, as used in this approach, OXA did not induce peripheral edema. In future studies we investigate alternate strategies to induce lower limb edema in the rat.

Sponsor: American Academy of Osteopathy
IRB/IACUC#: 2016-0045
Cytokine Responses to Cyclical Blood Flow Restriction Exercise

Introduction: We developed a novel adaptation of blood flow restriction exercise, cyclical blood flow restriction exercise (C-BFRE), as a method to potentially augment the cardio-protective effects associated with conventional exercise (CE) and remote ischemic preconditioning (RIPC). As the cytokines IL-6 and IL-10 have been implicated in mediating the acute cardio-protection associated with both exercise training and RIPC when performed independently, we hypothesized that C-BFRE would augment the systemic release of these factors compared to an acute bout of either CE or RIPC alone.

Methods: 13 young healthy subjects (6M/7F, age 28±2 y) completed 3 experimental sessions separated by at least 1 month each. Aerobic exercise was performed via 40-min of treadmill walking at 65-70% HR_{max} with (C-BFRE) and without (CE) application of bilateral thigh cuffs inflated to 220 mmHg (4 x 5-min inflation periods followed by 5-min reperfusion periods). RIPC consisted of 4 x 5-min thigh cuff inflation periods (220 mmHg) followed by 5-min reperfusion periods in the absence of exercise. Venous blood samples (via an antecubital vein) were collected at baseline and immediately following completion of each protocol for analysis of IL-6 and IL-10 via multiplex ELISA.

Results: Plasma IL-6 increased from baseline following CE (Pre, 0.26 ± 0.03 vs. Post, 0.40 ± 0.07 pg/ml; P=0.03) but not with C-BFRE (Pre, 0.28 ± 0.05 vs. Post, 0.34 ± 0.07 pg/ml; P=0.75) or RIPC (Pre, 0.31 ± 0.04 vs. Post, 0.32 ± 0.03 pg/ml; P=1.0). There were no changes in plasma IL-10 from pre- to post-intervention for any of the three conditions (P=0.42 for main effect of time).

Discussion: Contrary to our hypothesis, we observed no change in plasma IL-10 or IL-6 with application of acute C-BFRE. These findings suggest that the model of C-BFRE utilized in this study does not augment the release of these cytokines in young healthy individuals. This may be due to the timing of the blood samples, the use of a standard occlusive pressure across all subjects, and the young, healthy subjects tested in this study. Future work should delineate the inflammatory response induced by C-BFRE at more extended recovery time points, with use of individualized occlusive pressures, and in more clinically relevant populations in both acute and long term settings.

Sponsor: Funding for this study was provided, in part, by training fellowships awarded to Justin Sprick through a NIH-supported Neurobiology of Aging Training Grant (T32 AG020494, PI: Singh, M), and a Ruth L. Kirchstein NRSA F31 Predoctoral Fellowship (1F31HL1342

IRB/IACUC#: 2014-149
Effect of Acute Bilateral Vagotomy on Tissue-Specific Inflammation in a Murine Model of Systemic Lupus Erythematosus

Purpose: Chronic inflammation has been implicated in the pathogenesis of hypertension. We use a model of systemic lupus erythematosus (SLE) to study this relationship since SLE is a chronic autoimmune inflammatory disorder with a high prevalence of renal injury and hypertension. SLE is also associated with diminished autonomic (vagal) tone, and this implicates impaired neuroendocrine/neuroimmune mechanisms. One example is the classic hypothalamic-pituitary-adrenal (HPA) axis, which can be activated by the afferent vagus nerve and result in cortisol production and anti-inflammatory effects. Another example is the cholinergic anti-inflammatory pathway, an endogenous vagus nerve-to-spleen pathway that reduces inflammation upon stimulation. It is thought that both of these mechanisms are dysregulated and promote chronic inflammation in SLE. To confirm the importance of the vagus nerve in regulating inflammation though these mechanisms, we performed chronic unilateral vagotomy in SLE mice and determined that this paradoxically decreased inflammatory markers in the spleen and the kidney. We hypothesized that the other vagus nerve compensated and upregulated an anti-inflammatory response and that total vagotomy would exacerbate splenic and renal inflammation.

Methods: In the current study, anesthetized female SLE (NZBWF1) and control (NZW) mice (35 weeks of age; n=3 mice/group) underwent bilateral vagotomy and were euthanized 3 hours later, followed by tissue harvest.

Results: Spleen tumor necrosis factor (TNF)-a (measured by Western blot and normalized to total protein) was increased in SLE mice compared to controls (4.0e6 ± 2.2e6 vs. 1.5e6 ± 3.3e5; P=NS). Acute bilateral vagotomy exacerbated this inflammation in SLE mice (5.1e6 ± 2.5e6) and controls (3.2e6 ± 6.8e5). Renal cortical TNF-a was not different in SLE and control mice (7.4e5 ± 1.6e5 vs. 6.9e5 ± 4.8e4); however, acute bilateral vagotomy exacerbated TNF-a in SLE mice (1.3e6 ± 7.2e4 vs) and controls (1.2e6 ±6.5e5).

Conclusions: These findings suggest that the vagus nerve and vagally-mediated anti-inflammatory mechanisms like the HPA axis and the cholinergic anti-inflammatory pathway are critical in controlling inflammation in SLE. Future studies involving chronic bilateral vagotomy in SLE mice are necessary to confirm our hypotheses.

Sponsor: Studies supported by the AHA grant #14SDG18320033 to KWM and #16PRE29910012 to GSP as well as the NIH grant #1K01HL139859
IRB/IACUC#: 2017-0033
The Effect of Nicotinic Agonist Therapy on Renal Inflammation in Mice with Systemic Lupus Erythematosus

Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease that causes chronic systemic, and specifically renal, inflammation that results in renal injury and hypertension. Under normal conditions, inflammation may be regulated by a neuroimmune reflex referred to as the cholinergic anti-inflammatory pathway; this pathway is mediated by immune cells responding to acetylcholine via the a7-subunit of nicotinic acetylcholine receptors (nAChRs) and when stimulated results in the reduction of tissue-specific inflammation. These a7nAChRs can be activated nonselectively by nicotine and we have previously shown that nicotine attenuates renal inflammation in female SLE mice. However, because nicotine is toxic and addictive, it would not be available to use as a therapy for SLE. We hypothesized that a selective a7nAChR agonist would similarly reduce renal inflammation and protect against the development of renal injury.

Methods: In our pilot studies (n=2-3 mice/group), female SLE (NZBW/F1) and control (NZW) mice (33 weeks of age) were surgically implanted with osmotic mini-pumps to subcutaneously administer the nicotinic agonist PNU-120596 (3.8 mg/kg/day), or vehicle (100% DMSO) at a rate of 0.25 mL/hour. At 35 weeks, mice were euthanized and tissues harvested.

Results: The gene expression of renal cortical tumor necrosis factor (TNF)-a (measured by qRT-PCR using 2-ΔΔCt method normalized to HPRT) was found to be 3-fold higher in SLE mice as compared to control mice. However, PNU-120596 treatment did not have an effect on TNF-a gene expression in SLE or control mice. Renal cortical interferon (IFN)-a gene expression was similar in SLE and control mice. By contrast, PNU-120596 treatment increased IFN-a gene expression in both SLE mice and controls (18-fold and 3-fold, respectively).

Conclusions: Although inflammatory markers were increased in SLE mice, as expected, the effect of this PNU-120596 treatment on TNF-a and IFN-a is inconclusive, because statistical analysis was not performed due to the small sample size. Future studies will increase sample size and agonist dosage to further investigate the potential therapeutic effect of nicotinic agonists on SLE-induced inflammation and renal injury.

Sponsor: American Heart Association (14SDG18320033), National Institutes of Health (K01HL139859)
IRB/IACUC#: IACUC-2017-0033
Diagnosis and Management of Pyomyositis

Introduction: Pyomyositis is a purulent infection of striated muscle tissue that usually leads to an abscess, commonly due to S. aureus. The pathophysiology is unknown, but is proposed to be due to hematogenous bacterial seeding in muscle bodies. Pyomyositis is typically found in tropic regions, but it is increasingly being recognized in temperate climates, especially in immunocompromised individuals. Patient presentation ranges from afebrile with mildly elevated WBC to frank sepsis. In many reported cases, patients may develop multiple abscesses at different sites.

Case Description: A 54-year-old male with a history of COPD presented to the emergency department for worsening right pectoral pain with swelling and skin changes that persisted despite empiric outpatient antibiotic treatment for cellulitis. He reported superficial abrasions to the affected area one week prior to onset of symptoms along with fever, non-productive chronic cough, and red, swollen skin on his right chest. His social history was significant for heavy cigarette and alcohol use, and occasional methamphetamine use.

On admission, vital signs were unremarkable, but he soon developed fever and tachycardia. On exam, the right pectoral region and shoulder were erythematous and tender, and noticeably asymmetric. Lab results demonstrated elevated inflammatory markers. Initial ultrasound of the affected area was consistent with cellulitis. A CT scan demonstrated inflammatory stranding of the pectoral muscle but no abscess.

The patient was started on broad-spectrum antibiotics; however, his clinical status worsened. A repeat bedside ultrasound performed several days later demonstrated abscess formation. Surgical incision and drainage revealed copious purulence between the pectoralis minor and major muscles. Wound cultures grew methicillin-resistant S. aureus. The patient required repeat incision and drainage before being discharged on oral clindamycin.

Discussion: This case highlights the difficulty of detecting tropical pyomyositis in its early stages without strong clinical suspicion, and also points to a possibility that broad-spectrum antibiotics may not effectively treat early pyomyositis before abscess formation is achieved. The role of antibiotics in early tropical pyomyositis, therefore, may be to prevent continued hematogenous spread and subsequent appearance of further lesions, but may not impact progression of disease at the primary site.

Sponsor: N/A
IRB/IACUC#: 2018-076
Histoplasmosis Mistaken for Lung Neoplasm During Immunosuppression Therapy

Background

TNFα antagonists such as Cimzia use large immunogenic protein molecules to induce deviations in normal host immunity and inflammatory response. Most warnings address alert providers to seriously consider initiating immunologics, because TNF plays an important role in immunity, notably against mycobacteria. Cimzia is different than other prior agents targeting TNF, because it does not fix, complement or induce cell-mediated cytotoxicity that is antibody-dependent from not having an immunologic Fc portion.

Case information

A sixty year-old female with psoriasis, hypertension and greater than fifteen year history of Crohn's disease on Cimzia presented after four months of cough, night sweats, weight loss and generalized weakness. Her productive chronic cough evolved from brownish and bloody phlegm to a greenish color. Initial imaging from her PCP revealed a right upper lung mass thought to be a malignant tumor. Social history did not endorse any use of tobacco products or prior history of COPD, asthma or pneumonia. Family history for cancer was unremarkable. Patient describes that she was a teacher for many years in an older school building that had multiple past infestations, including possum. The initial attempt at bronchoscopy was inadequate for pathology, but repeated procedure denoted an exophytic and fungating mass. Cardiothoracic surgery performed an elective right partial right pneumonectomy and mediastinoscopy. Pathology performed on brushings were negative for malignancy, but endorsed a granuloma with acute inflammation. Final biopsy from the procedure revealed a granulomatous inflammation with a methenamine silver stain revealing histoplasmosis. Urine histoplasma antigen was negative, but antibody was high at 1:1, which can be seen with disseminated or diffuse pulmonary histoplasmosis. Patient began a short inpatient course of liposomal Amphotericin B transitioning to oral itraconazole prior to discharge.

Conclusions

Histoplasmosis mimics many common respiratory infections and neoplastic processes with symptom presentation and radiologic findings that have led to surgical resections of non-malignant pulmonary granulomatous nodules initially thought to be carcinomas. Patients on certolizumab should be closely monitored for the development of disseminated disease such histoplasmosis and warned about participating in activities that can expose them to inhalation of airborne microconidia.

Sponsor: N/A
IRB/IACUC#: MCFW-IRB
When Pigs Fly: Thromboembolic Events in a Case of Severe H1N1 Influenza Type A

Background/Abstract:

H1N1 Subtype Influenza Type A, the strain responsible for the 2009 pandemic, is primary regarded as a disease affecting lung parenchyma, yet it is its ability to infiltrate and cause system wide complications which has made it such a deadly virus. It is hypothesize the disease process may cause a propensity for thromboembolic events through activation of platelets, alterations of coagulation factors, or endothelial dysfunction. There have been multiple documented cases of pulmonary embolism and myocardial infarctions in prior reports in H1N1 infected individuals, but few of cerebral events. We present a unique case of severe H1N1-influenza in a previously healthy 47 year old male whose hospital course was complicated by multiple cerebral infarcts and R-femoral DVT.

Case Report:

47 year old caucasian male without a significant PMHx presented initially for fevers, myalgias, and respiratory distress requiring intubation at an outside facility. His condition worsened and was transferred to our facility for higher level of care. He was initially found to have septic shock requiring pressor support and started on empiric antibiotics. On arrival, the pt also underwent a bronchoscopy with washings; multiple cultures of blood, bronchial washings, sputum were negative for any growth. The pt continue to have breakthrough fevers. On admission day 4, he was found to have a DVT of R-femoral vein and started on a heparin drip; of note, the pt had been on chemical DVT prophylaxis since admission. Pt had difficulty with arousability off sedation and underwent extensive work-up including CSF studies which were negative. An MRI was significant for multiple small bilateral cerebral infarcts. Repeat transthoracic echoes were negative for signs of endocarditis or PFO on bubble study. Pt improved following tracheostomy placement and was discharged to LTAC on day 17th of hospitalization.

Discussion:

This case serves to illustrate the widespread effects of Influenza Type A H1N1 Subtype, even in healthy individuals. In this particular case, the pt had both venous and arterial thromboembolic events which is unique. It is important to keep in mind the extent of the disease process in this disease, especially in critically-ill patients.

Sponsor: N/A

IRB/IACUC#: MCFW-IRB
Plasma Biomarkers as Potential Indicators for HIV-associated Neurocognitive Disorders

Purpose: There are approximately 1.1 million people living with human immunodeficiency virus (HIV) in the United States (US). By race, African Americans and Hispanics are disproportionately affected by HIV. Despite improved life expectancy and a decline in HIV-associated dementia with the advent of antiretroviral therapy, HIV-associated neurocognitive disorders (HAND) remain a major comorbidity, affecting 15-50% of HIV+ individuals. HAND severity correlates with immune activation, suggesting that inflammatory mediators play a significant role in disease progression. This study aims to identify biomarkers which correlate to neurocognitive impairment and associate with gender and race.

Methods: HIV seropositive African Americans, Caucasians and Hispanics (10 men and 10 women in each category) were recruited in compliance with National Institutes of Health guidelines. Subject visits included informed consent, drug screening, HIV relevant medical history review, socio-demographic survey, neurocognitive assessment and blood collection. Neurocognitive assessment was further categorized into functional domains, domain 1 (memory, psychomotor speed, reaction time, complex attention and cognitive flexibility) and domain 2 (processing speed and executive functioning). Blood samples were processed to collect plasma, PBMCs, extra-chromosomal DNA, and RNA. Biomarker mRNA levels in PBMCs were quantified and protein levels were measured in plasma and PBMC culture supernatants. Differences in protein and mRNA levels across gender, cognitive status, race and socio-demographic factors were analyzed. HIV 2-LTR circles were quantified and correlated to neurocognitive status.

Results: Multivariate analysis identified monocyte chemoattractant protein 2 (MCP2) and tissue inhibitor of metalloproteinases 1 (TIMP-1) as significantly different across cognitive domain 1 and 2. Interleukin-10 was significantly different across cognitive domain 2. A significant difference by level of education, occupation and income was observed in cognitive domains 1 and 2. Univariate analysis was performed to identify specific domain tests, which correlated with neurocognitive status.

Conclusions: Our data suggest that plasma protein levels likely correlate with neurocognitive impairment. We also demonstrate a relationship between several socio-demographic factors and neurocognition. Further studies to characterize and validate these potential biomarkers as indicators of HAND are being conducted.

Sponsor: N/A
IRB/IACUC#: IRB-2010-063
Characterization of a doxycycline inducible and astrocyte-specific HIV-1 Nef transgenic mouse model (iNef)

Purpose: Over 37 million people worldwide are currently infected with human immunodeficiency virus type 1 (HIV-1). Introduction of combination antiretroviral therapy has improved the quality and length of life, leading to increased incidents of minor cognitive and motor disorder. HIV-1 infects astrocytes, the most abundant cells of the central nervous system (CNS). Once infected, astrocytes become reactive, characterized by increased expression of astrocyte-specific protein glial fibrillary acidic protein (GFAP). However, those cells do not support productive HIV replication, primarily expressing non-structural viral proteins, such as Tat and Nef. Although the role of Tat in HIV/neuroAIDS has been extensively studied, little is known about the roles of Nef in HIV/NeuroAIDS. Nef is known to play important roles in immune evasion, T-cell depletion, and disease progression. The current study is to characterize roles of Nef in HIV/NeuroAIDS.

Method: A doxycycline inducible astrocyte-specific HIV-1 Nef transgenic mouse model (iNef) was created. In this model, Nef expression is under the control of both GFAP promoter and doxycycline responsive elements, which allows characterization of the effects of Nef expression on the CNS, independent of HIV-1 infection. Neuropathological outcomes (astrocytosis, neuroinflammation, and neuronal integrity) and neurobehavioral effects (motor and memory) were determined using immunofluorescence staining and neurobehavioral batteries, respectively.

Results: Nef expression was confirmed in the brain of the iNef mice with doxycycline induction. Meanwhile, Increased GFAP expression and cytokine expression, loss of neuronal dendrites and decreased speed and latency to fall were found in these Nef-expressing iNef mice.

Conclusion: These data show that Nef expression led to astrocytosis, neuroinflammation, compromised neuronal integrity, and impaired coordination and motor function in Nef-expressing iNef mice and suggest that Nef could be a major contributing factor to HIV/neuroAIDS. Further investigation is under way to determine the underlying molecular mechanisms.

Sponsor: T32 AG020494. Grant: Institute of Healthy Aging, Pre-doctoral fellowship
IRB/IACUC#: IACUC-2016-0013
Molecular Genetics (Abstracts in the 1600s)

1600 - Poster

**Classification:** GSBS Student

**Presenter:** Gita Pathak

**Department:** Microbiology, Immunology, and Genetics

**Authors:** Gita A Pathak, MS, UNT Health Science Center; Nicole R Phillips, PhD, UNT Heath Science Center

**DNA repair polymorphisms and age-related diseases - Alzheimer’s and Cancer: Insights from SNP-set analysis and gene expression association**

**Purpose:** DNA repair response is a common thread for age-related diseases. Genomic stability is the result of an elaborate machinery consisting of damage response, repair, cell-cycle checkpoints, and apoptosis. A compromised DNA damage-repair response either due to time-dependent accumulation of damage or an individual’s reduced DNA repair capacity has been known to derail the genomic defenses, resulting in disease. Recent research findings and epidemiological studies speculate an inverse association between Alzheimer’s and cancer. Since impaired DNA repair is known to accelerate age-related disease, our goal is to evaluate DNA damage/repair genes and identify the role of DNA repair polymorphisms in Alzheimer’s, Breast and Prostate Cancer in individuals.

**Methods:** The raw genotype and phenotype data were obtained via authorized access application for Alzheimer’s Disease Neuroimaging Initiative and Breast and Prostate Cancer Cohort Consortium; genotype data were generated using the Illumina Human Quad610™ Beadchip. Controls with positive family history were removed; all subjects used were >50 years. Data were processed with in-house codes for QC, mapping SNPs to genes and extracting SNP sets based on 274 candidate genes. SNPs within each set were tested (permutation protocol, mperm=5000) and interpreted for biological relevance after correcting for multiple set-tests. Association analyses accounted for key covariates such as age and sex. Results with genomic inflation of more than 1.03 were adjusted using first three eigenvectors as covariates. Gene expression was imputed for candidate genes. Analyses were performed in Plink(v1.9), EIGENSOFT-6.4, Rstudio 3.4, Bioconductor 3.6, VEGA2, Python 3, PrediXcan and MAGMA.

**Results:** After two-level QC filtering, the datasets – ADNI, Breast and Prostate cancer – had 677, 578 and 3857 individuals, respectively. Gene-sets of ~167 genes were created for each dataset. Preliminary results point to cancer-specific variants in key DNA repair genes, some of which have not previously been reported. Structured sets of DNA repair pathways and gene expression imputation are in the analysis phase.

**Conclusion:** This study investigates DNA repair genes in both cancer and Alzheimer’s using SNP-set analysis to improve detection of association that sometimes get lost in whole-genome associations. Our results provide a detailed overview of various DNA repair genes and their association with complex phenotypes of age-associated diseases.

**Sponsor:** Neurobiology of Aging Training funded by NIH training grant T32 AG 020494

**IRB/IACUC#:** 2016-090
Mitochondrial dysfunction and DNA methylation in type 2 diabetes and cognitive impairment

Background. Mexican American populations are disproportionately affected by type 2 diabetes (T2D) and Alzheimer’s disease (AD). Although commonly characterized by the accumulation of amyloid plaques and tau tangles, the role of mitochondrial dysfunction (changes in mitochondrial dynamics, apoptosis, and/or oxidative stress signaling) in AD pathophysiology has become further elucidated over recent years. Methylation of key nuclear-encoded genes may be involved in regulation of critical mitochondrial processes. Evidence suggests that differential methylation and expression of mitochondrial related genes (e.g. \textit{POLG}) may correlate with mitochondrial DNA copy number (mtDNA\textsubscript{CN}).

Hypothesis. We tested the following hypotheses: (1) methylation of mitochondrial-related genes is negatively correlated with their respective gene expression, (2) methylation of mitochondrial biogenesis genes (e.g. \textit{TFAM}, \textit{POLG}) negatively correlates with mtDNA\textsubscript{CN} per cell, and (3) methylation of genes related to oxidative stress response, mitophagy, endosomal/exosomal trafficking and apoptosis correlates with cell-free mtDNA (mtDNA\textsubscript{CF}) levels.

Methods. DNA from 14 female Mexican American subjects enrolled in HABLE, the Healthy Aging Brains of Latino Elders cohort, was used for this study. Subjects were grouped based on T2D diagnosis, and were matched across groups based on age and cognitive status. For mitochondrial-related gene expression, cDNA was synthesized from blood buffy coat RNA and tested using the RT\textsuperscript{2} Profiler™ Human Mitochondria Array. For methylation analysis, nDNA from the blood buffy coat extract was bisulfite-converted and methylation levels were determined using the MethylationEPIC™ beadchip. Data was analyzed using Genome Studio. Buffy coat mtDNA\textsubscript{CN} and plasma mtDNA\textsubscript{CF} were quantified using TaqMan®-based qPCR. Methylation levels of CpG regions around candidate genes were then correlated with (1) gene expression, (2) mtDNA\textsubscript{CN}, and (3) mtDNA\textsubscript{CF}.

Results. Preliminary results indicate that hypomethylation of some mitochondrial-related genes corresponds with increased expression (e.g., \textit{COX10}); methylation of two sites associated with a known CpG island for \textit{POLG} are negatively correlated with mtDNA copy number per cell.

Conclusions. Significant correlations between mitochondrial phenotypes and candidate gene epigenetic loci may point to novel regulatory mechanisms of mitochondrial function. Future studies will include exploratory analysis at the genome-wide level using a larger cohort.

\textbf{Sponsor:} N/A

IRB/IACUC#: #2012-083
Pilot Study Using the Tail Suspension Test

Purpose:
The Porsolt Swim Test (PST) is an established protocol to study the antidepressant-like effect of potential CNS agents. The purpose of this study is to introduce a complimentary behavioral model to assess this central effect; specifically, in this study, we implemented the Tail Suspension Test (TST) to our lab. The validation of the TST model was performed by exploiting the well-known antidepressant-like effect of thyrotropin releasing hormone (TRH) in a comparative fashion with that of the PST.

Method:
We constructed an apparatus to perform the TST where mice are suspended by their tails. The motionless hanging of an animal is associated with a depressive state, and the time an animal spends in this state is called immobility time. In the PST, on the other hand, an animal is placed in an inescapable water-filled cylinder, and immobility time is defined as when an animal only makes minimal movements to keep its head above the water. To validate the newly introduced TST, CD1 mice received either vehicle or various concentrations of TRH via dorsal s.c. injection 30 min before testing in both paradigms. Two independent observers measured immobility time for the duration of the experiment, after which animals were sacrificed and tissues harvested for future TRH quantification. Mice were only exposed to these experimental conditions on the day of the experiment and each mouse was only subjected to a single dose and subsequent test -no preconditioning was required.

Results:
Comparisons of the TRH-treated groups and the control group showed a statistically significant difference in immobility time, indicating the antidepressant-like effect of this small neuropeptide. A dose-dependent reduction of immobility time was observed in both the PST and the TST; moreover, the calculated $ED_{50}$ values were not significantly different from each other. Specifically, $ED_{50}$ was approximated at 2 µmol/kg body weight in the PST, and about 1.5 µmol/kg body weight in the TST.

Conclusion:
We have successfully implemented the TST, a complimentary paradigm to the PST, to study potential antidepressant-like agents. Moreover, we have also shown that TRH, a neuropeptide with well-known antidepressant effect exhibits similar potency in both experimental paradigms.

Sponsor: Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R25HL125447 (to Dr. J.K.Vishwanatha) and by a UNTHSC Intramural Grant (to Dr. K. Prokai-Tatrai).
IRB/IACUC#: 2014/15-20-A04
Influence of exogenous oxidative stress on the resilience of aged glutathione-deficient mice

Introduction

With age, individuals become less resilient against stressors, rendering them more susceptible to diseases and leading to exacerbated brain impairments. Aging also involves a shift in redox state that can be associated with the key molecule, glutathione. To determine the importance of glutathione in stress resilience, we sought to study the effect of an oxidative stressor (paraquat) in an animal model of chronic glutathione deficiency. Glutathione deficiency can be achieved by the genetic knockout of the modifier subunit of the enzyme, glutamate cysteine ligase (gclm). Our hypothesis was that chronic glutathione deficiency will render mice less resilient to the oxidative stress induced by paraquat and will cause further impairments in motor and cognitive function.

Methods

Old (18 months) male and female gclm+/+ and gclm-/- mice received one to two intraperitoneal injections of 10 mg/kg of paraquat (PQ) or saline for one week. Four days following the last injection, animals underwent behavioral tests measuring affective, cognitive and motor function (locomotor activity, elevated zero maze, bridge walking, wire suspension, fear conditioning, rotorod, and active avoidance). After the completion of behavioral testing, brain regions, skeletal muscle, liver, heart, and kidney tissues were harvested and will be used to examine biochemical changes in oxidative damage and redox signaling. The data were analyzed using 2 or 3-way ANOVAs followed by pairwise comparisons.

Results

Body weights in male and female mice dropped immediately after PQ injection, with the gclm-/treatment group having a greater decrease in percentage of body weight than the gclm+/+. PQ injections appeared to decrease overall activity of both gclm+/+ and gclm -/-. PQ-treated mice seemed to spend less time in open arms, indicating increased anxiety levels. Overall, PQ-treated mice appeared to perform better on motor skills and worse on cognitive tests.

Conclusions

These preliminary data suggest a trend that paraquat may have differential effects depending on the task (cognitive vs. motor), and gclm -/- mice may be more susceptible to an oxidative stressor.

Sponsor: P01 AG027956, T32AG020494 (NIH/NIA)
IRB/IACUC#: 2014/15-37-A04
Inline flow sensor for ventriculoperitoneal shunts: Experimental evaluation in swine

Background:
Hydrocephalus is a potentially life-threatening disorder in which cerebrospinal fluid (CSF) fails to circulate properly, causing a dangerous buildup of pressure in the cerebral ventricles and the surrounding brain tissue. It is seen most often in infants with congenital abnormalities of the CSF tract, and in patients with traumatic brain injury. The only treatment in most cases is the placement of a tubing to drain the excess CSF from the brain to the abdomen. These shunts are prone to blockage that requires invasive replacement surgery, so a reliable flow sensor is needed to detect shunt failure at its early stages. Currently available flow sensors often fail to detect blockage.

Objective:
The purpose of this project is to evaluate an advanced in-line electronic flow sensor capable of monitoring CSF flow over time for use in the treatment of hydrocephalus. This project evaluated the performance of this sensor in domestic swine.

Methods/Materials:
Ventriculo-peritoneal shunts were installed in the third cerebral ventricle of juvenile Yorkshire pigs, and routed to the peritoneal space in the abdomen. The flow sensor was positioned halfway between the cephalic and peritoneal ends of the shunt. Data were acquired on a laptop computer. Shunt flows were obtained at 30 s intervals. The sensor alternately heated the shunt fluid for 5 s and then monitored temperature decline, the rate of which was proportional to flow, for 25 s. The fluid was diverted into pre-weighed vials for 1- or 5-min to determine flow gravimetrically. At regular intervals, 5-20 ml boluses of artificial CSF were injected into the third ventricle. Flows reported by the sensor were compared to concomitant gravimetric flows by linear regression.

Results:
Over 4300 sensor measurements of flow were obtained in 6 experiments. The flow sensor reliably reports shunt flows up to 35 ml/min, the highest rate produced by 20 ml CSF injections. Four experiments showed strong linear correlations ($r^2 > 0.90$) between gravimetric and sensor flows. The slope of the linear regression between the two flows was $1.05 \pm 0.14$ in the 6 experiments, indicating that the sensor accurately reported flows of up to 35 ml/min.

Conclusions:
The results of this experiment indicate that the flow sensor can report accurately ventriculo-peritoneal shunt flows over a wide range in a large animal model. Studies are planned to evaluate performance of chronically implanted shunts in ambulatory pigs.

**Sponsor:** Funding: Texas Medical Research Consortium, Dane Eskildsen was supported by the TCOM Honors Research Practicum  
**IRB/IACUC #:** IACUC-2017-0029
Development and Use of “Sniffer Cells” to Detect the Presence of Neuropeptides

Purpose:

The brain is sensitive to Angiotensin (Ang) II and expresses the enzymes necessary for synthesis. However, neuropeptide release has historically been difficult to study and it is currently unclear if Ang II is utilized as a neurotransmitter within the brain. To address this question, our laboratory has adopted a relatively new approach to study the brain renin-angiotensin system – sniffer cells.

Methods:

To make the sniffer cells, Chinese Hamster Ovary (CHO) cells were transfected with plasmids to express angiotensin type 1a (AT1a) receptors and a genetically encoded fluorescent Ca2+ sensor (GCaMP or R-GECO) to address the mechanisms of brain angiotensin II release. Sniffer cells were plated on glass cover slips and continually perfused with aCSF. Calcium imaging was performed at 2 sec intervals using excitation/emission wavelengths of 488/525 nm (GCaMP) or 589/615 nm (R-GECO) and fluorescent intensity was measured in response to bath application of neuropeptides. Sniffer cells were also placed on the median preoptic nucleus (MnPO) in in vitro brain slices (produced using standard slice procedures) from male Sprague-Dawley rats (250-300 g). Fluorescent intensity was measured at 1 sec intervals in response to electrical and optogenetic stimulation of the subfornical organ (SFO).

Results:

The sniffer cells exhibit an increases in fluorescence in response to exogenously applied Ang II that is blocked by the AT1aR antagonist Losartan. The observed increases in fluorescence was specific to AT1aR activation as exogenous application of other common neurotransmitters (Glutamate, Glycine, GABA, NE, ACh) failed to increase sniffer cell. The intensity of sniffer cell responses to Ang II and Ang III were dose dependent with the sniffer cells being more sensitive to Ang III. Using these sniffer cells we were able to detect spontaneous release of Ang II in the MnPO (n = 63). The spontaneous release was activity dependent (i.e. blocked by TTX, n = 10). We were also able to evoke release of Ang II onto sniffer cells via both electrical stimulation (n = 5) and optogenetic stimulation (n = 23) of the SFO.

Conclusion:

Using sniffer cells we were able to detect release of Ang II from in vitro brain slices. Future studies using these sniffer cells will 1) verify the existence of the brain-renin-angiotensin system, 2) characterize the phenotype of Angiotensin II releasing neurons, and 3) investigate potential changes in brain Angiotensin II release in sleep apnea. Sniffer cells are a useful tool for the detection and quantification of neuropeptide release in in vitro neuronal slice preparation and may offer utility in other applications.

Sponsor: Nat Heart, Lung & Blood Institute 1 R01 HL119458-01A1
IRB/IACUC#: 2014/15-29-A05
Positive allosteric modulation of alpha7 nicotinic acetylcholine receptors as a novel approach to treatment of ischemic stroke

Ischemic stroke is a leading cause of disability and death worldwide. Despite substantial investments in developing anti-stroke medicines, clinically effective pharmacological treatments remain inadequate. Clinical utility of tissue plasminogen activator (tPA, Alteplase), the only FDA-approved drug treatment is limited (72 h) intravenous (i.v.) or subcutaneous (s.c.) administration of PNU significantly reduced brain injury and neurological deficits after MCAO. The therapeutic efficacy of PNU after stroke may arise from activation of multiple converging α7-dependent therapeutic pathways including direct cytoprotection and central/peripheral anti-inflammatory mechanisms and may hold significant translational potential. Our results may become a starting point for developing clinically efficacious therapies utilizing α7 agents and may enable health-care providers to overcome limitations linked to the lack of effective treatments after stroke.

Sponsor: N/A
IRB/IACUC#: 2017-0004
INTERACTIONS BETWEEN T-CELLS AND ASTROCYTES POST-ISCHEMIC STROKE

Purpose: In post-ischemic stroke, T-lymphocytes enter the brain. Presently, the role of these T-cells in the progression of cerebral infarction or repair mechanisms is unclear. Our goal is to analyze the function of T-cells in regions of cerebral infarction by examining the pro- and anti-inflammatory interaction between T-cells and brain cells within these lesions.

Methods: Ischemic stroke was induced by middle cerebral artery occlusion in young adult C57/B6 male mice. Mice were sacrificed at 3 days or 1-month post-ischemic stroke. T-cells were harvested from the brain by digestion; percoll enriched, and incubated with anti-CD3 and CD25 antibodies. T-cells were sorted via flow cytometry. The cytokine expression profile of brain infiltrated T-cells was compared to spleen T-cells using q-RTPCR.

Results: In this in vivo study the following cytokines, poststroke, were found to be elevated: IFN-γ, IL-10, IL-17, TNFα, Perforin, T-bet, and RORc.

Conclusions: Our data suggests that understanding the interaction between T-cells and astrocytes could open new therapeutic strategies for stroke patients.

Sponsor: National Institutes of Health grants 1R21NS087209-01A1, R01NS088596, and Neurobiology of Aging T32 AG020494.

IRB/IACUC#: IACUC – 2017-0021
Tissue Plasminogen Activator-Porous Magnetic Nanorods for Targeted Thrombolytic Therapy after Ischemic Stroke

Purpose: Stroke is the 5th leading cause of death in the US. The only FDA-approved treatment is the intravenous administration of tissue plasminogen activator (tPA). However, due to tPA’s inability to lyse the clot fully, about 90% of these patients still live with speech or motor impediments. Moreover, the large dose of tPA administered increases the susceptibility to global tPA-mediated hemorrhage. Therefore, the purpose of the study was to increase tPA’s thrombolysis rate and reduce total tPA administered using a novel nanomaterial, tPA-loaded Fe₃O₄ nanorods (tPA-NRs). We hypothesize that tPA-NRs will be more successful at thrombolysis and minimize the off-target effects of tPA.

Methods: Fe₃O₄ nanorods were fabricated by oblique angle deposition technique and loaded with tPA using glutaraldehyde as the cross-linker. To determine the thrombolysis efficiency of tPA-NRs in vitro, PE50 catheters containing blood clots were used as the vascular thrombosis model to mimic in vivo thrombotic conditions. Such PE 50 catheters containing blood clots were placed vertically in the center of a rotating magnetic field and the blood clot lysis time was recorded. To examine the proposed approach in vivo, a FeCl₃-induced distal middle cerebral artery occlusion (dMCAO) model was used. Animals will randomly be assigned to four groups and treated with tPA-NRs (1 mg/kg), NRs (1 mg/kg), tPA (10 mg/kg) or vehicle accordingly via internal carotid artery injection after ischemic stroke. A custom-made rotational magnetic field was applied above the head of mouse (near infarction region) during and after injection for 60 min, and the thrombolysis process was observed under microscope.

Results: In vitro results demonstrated that tPA-NRs could achieve a mass loading ratio as high as 12.9% and the loaded tPA can be released when stimulated by an external rotating magnetic field. Furthermore, PE50-catheter thrombolysis results demonstrated that tPA-NRs had a significant enhancement of thrombolysis efficiency in comparison with high-dose tPA group (P < 0.001). In vivo results unequivocally showed that: 1) intra-arterial injection of tPA-NRs could target the site of the clot under magnetic guidance; 2) the mechanical force generated by the spinning of the tPA-NRs under the external rotational magnetic field could significantly decrease dMCA blood flow recanalization time from 85 min with high dose tPA (10 mg/kg) to 25 min with low dose tPA-NRs (1 mg/kg) (p < 0.001). Importantly, intravenously injected NRs could be discharged from the kidney, and the function of liver and kidney were not damaged at different durations after administration of tPA-NRs.

Conclusions: In summary, this study provides a proof of concept for developing novel, biocompatible, magnetically guided tPA-NRs delivery system to enhance thrombolysis after ischemic stroke. This approach is significant in that it could not only revolutionize for the treatment of ischemic stroke but also have major impacts on treatments for other deadly thrombotic diseases such as myocardial infarction and pulmonary embolism.

Sponsor: N/A
IRB/IACUC#: IACUC-2016-0051
Neurocognitive decline and dysregulation of Astrocyte-TIMP-1 in a Tat-transgenic mouse model

Purpose: Despite antiretroviral therapy, HIV-associated neurocognitive disorders (HAND) persist in 60-70% of patients. In the brain, HIV-1 non-productively infects astrocytes, which produce and release HIV-1 proteins such as transactivator of transcription (Tat). Tat induces neuronal death and inflammation by direct and indirect mechanisms. During HAND, elevated matrix metalloproteinases (MMPs) aid ECM breakdown facilitating disease progression; whereas, tissue inhibitors of MMPs (TIMPs) impede their activity. Astrocyte TIMP-1 is an inducible protein and its neuroprotective effects have been shown. Astrocyte TIMP-1 expression increases with acute neuroinflammation in vitro, but its levels are reduced during chronic inflammatory brain diseases; indicative of a concomitant loss of TIMP-1 mediated neuroprotection. However, little is known about Tat regulation of astrocyte TIMP-1 expression. We hypothesize that HIV-1 Tat downregulates astrocyte TIMP-1 and induces inflammatory changes that contribute to neurocognitive decline.

Methods: A doxycycline-inducible, glial fibrillary acidic protein (GFAP) promoter-restricted HIV-1 Tat mouse model (GT-Tg) was used to investigate astrocyte associated disease mechanisms. Neurocognitive decline was assessed using a battery of behavior tests in GT-Tg and wild-type (WT) mice. Subsequently, mouse brains were harvested to evaluate gene and protein expression.

Results: GT-Tg mice had higher anxiety and lower initiation latency in elevated plus maze and locomotor activity tests, respectively. While GT-Tg mice swam faster in Morris water maze, latency and pathlength were comparable to WT. Discriminated reversal test and novel object recognition did not differ significantly between GT-Tg and WT mice. Although TIMP-1 gene expression was elevated in GT-Tg verses WT mice, it negatively correlated with Tat expression consistent with human astrocytes chronic responses. Gene and protein expression for other inflammatory biomarkers and GFAP were evaluated, and correlated with Tat expression.

Conclusions: Collectively, our data from GT-Tg mouse model confirmed that TIMP-1 dysregulation is associated with neurocognitive decline in the context of HAND suggesting replenishing TIMP-1 levels could be used as a novel therapeutic option.

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IRB/IACUC#: 2007-121; 2017-0017
Connexin 43 as a Mediator of Androgen and Estrogen-induced Protection against Oxidative Stress in Astrocytes

Purpose: Connexin 43 (Cx43) is a transmembrane protein highly expressed in astrocytes, whose expression and/or channel permeability can impact cell viability in the presence of oxidative stress. Androgens and estrogens are also known to protect against oxidative stress. However, it remains unknown whether these hormones alter Cx43 channel expression or permeability as a mediator of their protective effects. Here, we propose that the androgen, dihydrotestosterone (DHT) and the estrogens, E2 and 3betadiol (the latter being a metabolite of DHT), protect against oxidative stress in astrocytes through the regulation of Cx43 expression and/or permeability.

Hypothesis: Reducing the permeability of Cx43 gap junctions or Cx43 hemichannels enhances the protective efficacy of E2, DHT, or 3betadiol against oxidative stress in cerebral cortical astrocytes.

Methods: Using cortical astrocytes from neonatal female C57/Bl6 mice and the astrocytic C6 glioma cell line, we assessed changes in Cx43 mRNA expression, Cx43 permeability, and cell viability following treatment with 100 nM E2, DHT, or the DHT metabolite, 5-alpha-androstane-3-beta,17-beta-diol (3betadiol), and compared it to the effect of the vehicle (DMSO) control, in the presence or absence of the metabolic and oxidative stressor, iodoacetic acid. Changes in Cx43 mRNA expression relative to GAPDH were assessed by RTPCR; The MTT assay was used to assess cell viability under conditions of metabolic/oxidative stress, with or without the pharmacological manipulation of Cx43 channels; changes in Cx43 hemichannel permeability were assessed using the Ethidium Bromide dye uptake assay.

Results & Conclusions: While only E2 transiently increased astrocyte Cx43 mRNA expression, E2, DHT, 3betadiol each blocked IAA induced increase in Cx43 hemichannel permeability to an extent similar to the hemichannel antagonist Boldine. Given that Boldine-induced hemichannel blockade significantly protected cells from oxidative stress, hemichannel blockade may also be a component of these steroids’ protective mechanisms. These data indicate that enhanced Cx43 hemichannel permeability not only inhibits the protective effects of E2 or DHT, but that the protective effects of E2 and DHT may be mediated, at least in part, by the regulation of Cx43 hemichannel permeability.

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IRB/IACUC#: 2014/15-49-A05
Using human pluripotent stem cell-based models to understand a congenital deglycosylation disorder-induced abnormality in cerebral development

Background: Human pluripotent stem cells (hPSCs) provide significant promise for regenerative medicine and in addressing questions relevant to the disease physiopathology. Therefore, the generation of hPSCs using somatic cells obtained by noninvasive approaches would be ideal for securing patient samples and further implement the notion of personalized insight into disease and treatment. Neurodysfunction caused by a congenital disorder of deglycosylation, NGLY1 deficiency, was recently identified. How NGLY1 deficiency disturbs normal cerebral development and causes neurological abnormalities in the pediatric population is unknown.

Purpose: Our desire is to establish a hPSC-based disease model of NGLY1 deficiency and study the pathogenic neurogenesis associated with NGLY1 loss and its influences on early development of the human brain.

Method: Urinary epithelial cells from urine specimens of normal individuals and patient skin biopsy-derived fibroblasts were collected and reprogrammed to generate transgene-free human induced pluripotent stem cells (hiPSCs). Through gene editing, NGLY1-deficient hPSCs were obtained from the normal hPSCs which included human embryonic stem cells (hESCs) and hiPSCs. The NGLY1-deficient hPSCs and their normal counterparts were differentiated into neural cells using 2D- and 3D-differentiation protocols optimized by our group. Systems biology and 3D-imaging techniques were employed to characterize the cellular and molecular features of NGLY1-deficient neurodevelopment.

Results: Urine-derived hiPSCs were pluripotent and capable of forming cerebral organoids that contain multiple types of neural cells in a self-organized and layered 3D structure closely mimicking the early human forebrain development. Like normal hPSCs, NGLY1-deficient hPSCs also form cerebral organoids. Unique gene expression patterns in NGLY1-deficient samples at different stages of development were identified by transcriptomic analysis. Structural abnormalities were also observed in NGLY1-deficient organoids compared with normal organoids.

Conclusions: We have streamlined the production of cerebral organoids using hiPSCs reprogrammed from non-invasively collected cells via urine specimens and NGLY1-deficient hPSCs. Additionally, we demonstrate our ability to recapitulate NGLY1 deficiency down to the molecular level, and to continually uncover insights into a pathologically enigmatic disease. In doing so, we clearly exemplify a beginning to end approach that can be used to study other neurological diseases, as well as, assay their potential therapies in an all human-based and personalizable system.

Sponsor: N/A
IRB/IACUC#: 2014-101
Moyamoya Disease Presenting as Subarachnoid Hemorrhage without Cerebral Aneurysm

Background: Moyamoya Disease (MMD) is a rare cerebrovascular disease caused by progressive stenosis or occlusion of the distal portion of the internal carotid arteries and/or the major cerebral arteries that arise from it. The stenosis triggers the development of an abnormal network of compensatory vessels to maintain cerebral blood flow. Subarachnoid hemorrhage (SAH) is a rare presentation of MMD, and non-aneurysmal subarachnoid hemorrhage is extremely rare, with only six previously documented cases worldwide. Our case report is an example of this extremely rare case presentation.

Case Description: In this report, we describe the case of a 52-year-old male who suddenly developed severe headache and loss of consciousness after sexual intercourse. CT scan revealed SAH over the left frontal and temporal cortex. Cerebral angiogram demonstrated no aneurysm, but high grade narrowing of the left middle cerebral artery (MCA) and collateral blood flow from surrounding cerebral arteries consistent with moyamoya disease. The patient was managed medically throughout his hospital course and remained neurologically intact with no further hemorrhagic events. He was referred to neurosurgery outpatient for evaluation of revascularization surgery.

Conclusions: Non-aneurysmal SAH in moyamoya disease is extremely rare. The evidence from this case, as well as the literature, supports the hypothesis that it is due to rupture of fragile transdural anastomotic vessels on the brain surface as they traverse through the subarachnoid space. An understanding of this unique mechanism of disease is valuable not only for tailored management, but also for considerations in surgical approach to revascularization.

Sponsor: N/A
IRB/IACUC#: 2018-066

Purpose: Antiretroviral therapy (ART) has extended lifespans by decades for HIV-infected individuals. However, the prevalence of HIV-associated neurocognitive disorders (HAND) continues to be high despite successful ART therapy. Brain astrocytes can harbor provirus and express neurotoxic HIV proteins such as gp120 and TAT, potentially contributing to HAND. In addition, neurocognitive decline is exacerbated in individuals who use methamphetamine (METH). We hypothesize that METH treatment in gp120+ mice will cause changes in gene expression and damage/death to specific cell populations.

Methods: To examine the role of METH in HAND, we used a transgenic mouse line expressing GFAP-controlled HIV gp120 protein (gp120+). Mice were injected intraperitoneally with either 0.9% saline vehicle or successive weekly escalating doses of 1, 5, 10, or 30 mg/kg METH, and their brains were harvested 7 days post-injection for qPCR, immunohistochemistry and protein analyses.

Results: In qPCR experiments, gp120+ mice showed dramatically increased levels of GFAP mRNA, suggesting chronic gp120 expression causes astrocyte activation. However, a qPCR probe designed to distinguish the transgene versus the endogenous GFAP transcripts showed lower levels of GFAP activation, suggesting that some of the GFAP mRNA expression is read-through from the transgene construct. GFAP expression in the rostral portion of the brain (anterior to ~0 bregma) was lower than the caudal portion in the gp120- mice, whereas GFAP was higher in the rostral portion in the gp120+ mice, suggesting enhanced astrocyte activation in the rostral portion of the brain encompassing the striatum and frontal cortex. Tissue inhibitor of metalloproteinase-1 (TIMP1) and interleukin 1-beta (IL1b) mRNA levels were increased in gp120+ mice compared to gp120- mice. Gene expression levels of excitatory amino acid transporter-2, tyrosine hydroxylase, and dopamine transporter were not changed in gp120+ mice. None of the METH treatments changed in gene expression in either mouse group at 7 days post-injection.

Conclusions: Long-term expression of gp120 in brain leads to altered gene expression of neuroinflammatory mediators. Single-dose METH treatment did not alter gene expression for the targets studied in either the gp120- or gp120+ mouse lines. Future experiments will focus on changes in protein expression and functional properties of specific cell populations in the brain at different times post-METH treatment.

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IRB/IACUC#: 2014/15-38-A04
Influence of ovarian hormone deprivation length on the neuroprotective effects of genistein in stroke

Purpose: Estrogen deprivation increases the risk of stroke, cardiovascular disease, and cognitive decline in women. Studies in rats demonstrate that the beneficial effects of estrogen in the brain are lost 10 weeks after Ovx. Similar effects are seen in women after several years without estrogen. Thus, most benefits require early intervention with hormones after menopause. Unfortunately, estrogens also have undesirable effects (such as breast cancer) that lead women to alternative treatments for menopause, including plant estrogens such as genistein. Natural products are perceived to be safe even though their benefits are not well established. This project sought to investigate genistein’s ability to protect the brain at varying lengths of ovarian hormone deprivation.

Hypothesis: Dietary genistein will maintain the ability to provide neuroprotection in the brain and improve functional recovery after long-term hormone deprivation associated with ovariectomy (Ovx).

Method: Adult female Sprague-Dawley rats (n=6-8) were bilaterally ovariectomized and randomly assigned to 2- (Short, ST) or 12-weeks (Long, LT) estrogen deprivation before starting diets with no isoflavone or genistein (500 ppm) for the rest of the study. After 6 weeks on diets, all rats were subjected to 60 minutes transient middle cerebral artery occlusion (MCAO) or sham surgery. Neurological (neuroscore), motor (rotarod) and cognitive function (Morris water maze, MWM) were used to assess post-MCAO function over 21 days. Rats were humanely euthanized for biochemical and histological follow-up. Data was assessed with 2-way ANOVA and significance set at p<0.05.

Results: Neuroscore showed a significant effect of stroke, but not diet, in both ST and LT with the LT group performing worse than the ST group (P=0.06). Rotarod showed a significant effect of stroke, but not diet, on learning phase performance for the ST group and a significant interaction between diet and stroke on the learning phase in the LT group. Comparison between ST and LT stroke subgroups showed a significant effect of diet in the learning phase of rotarod. MWM tests are ongoing and suggest that genistein improves performance in the ST groups.

Conclusion: Results from these preliminary studies suggest that long-term estrogen deprivation enhances the detrimental behavioral effects of stroke. In sensory-motor assessments, dietary genistein had little effect but may be beneficial for post-stroke cognitive behavior.

Sponsor: J. E. S. Edwards Foundation

IRB/IACUC#: 2016-0040
Cholesterol sulfate alters astrocyte metabolism and offers some neuroprotective effects

Introduction: Cholesterol sulfate (CS) is one of the most important known sterol sulfates in human plasma and present as a normal constituent in a variety of human tissues. In both the brain and periphery, CS serves as a substrate for the synthesis of sulfonated adrenal steroids such as pregnenolone sulfate and Dehydroepiandrosterone (DHEA) sulfate and as a constituent of many biological membranes including red blood cells where it functions as a stabilizing agent. It also acts as endogenous regulator of cholesterol synthesis. It is known that CS serves as a substrate for synthesizing other sterol sulfates in the brain. However, the role of CS in neurological insult and brain metabolism is unknown. Our goal in this study is to investigate the neuroprotective action of CS as well as its effect on brain energy metabolism.

Materials and Methods: Primary astrocytes were prepared from the cortex of postnatal day 0-2 C57BL/6 pups and seeded in Dulbecco’s modified eagle medium (DMEM) with 10% FBS under normal glucose (5.5 mM). HT-22 cells were maintained in high glucose (25 mM) DMEM supplemented with charcoal stripped FBS. The neuroprotective effect of CS and its role on cell metabolism were determined in primary astrocyte and HT-22 cells using Calcien AM cell viability assay, flow cytometry, seahorse extracellular flux analysis, and metabolism assay kits.

Results: CS protects HT22 cells against glutamate toxicity and impact astrocyte metabolism by increasing ATP, and glycogen contents.

Conclusion: Our study demonstrated that CS have neuroprotective effect and modulate brain energy metabolism. Further studies are needed to determine the mechanisms underlying the neuroprotective action of CS and its action on brain energy metabolism.

Sponsor: NIH
IRB/IACUC#: 2013/14-43-A04
The Role of Testosterone Deprivation and Replacement on Stroke Outcome in Middle-Aged Rats

Background: Circulating levels of the steroid hormone testosterone fall in aging men, and in the last decade the number of men obtaining prescriptions for testosterone replacement therapy (TRT) has increased dramatically. However, other consequences of aging, such as increased oxidative stress, may result in detrimental effects when combined with TRT. This include increased risks of thromboembolism and stroke. In women, a delay in hormone therapy (estrogen/progesterone) after menopause results in a loss of benefit for the brain and an increase in risk for stroke and cognitive decline. Whether such a delay would alter the effects of TRT is not known.

Hypothesis: In this study, we hypothesized that a delay in TRT following castration in middle-aged male rats would result in increased oxidative stress and a reduction in the neuroprotective effects of testosterone following stroke (transient cerebral ischemia).

Methods: Twelve-month old male Fischer 344 rats were obtained from the National Institutes on Aging. Rats were divided into 5 groups as follows: 1) gonad Intact sham stroke (SHAM), 2) Intact stroke (INT), 3) short term castrate + TRT (STT), 4) long term castrate (LT), and 5) long term castrate + TRT (LTT). Rats were castrated 2 weeks (STT) or 10 weeks (LT, LTT) prior to TRT by subcutaneous silastic capsules containing T. L3T rats were treated with the antioxidant TEMPOL in drinking water starting 2 weeks before TRT. Middle cerebral artery occlusion (Stroke) was accomplished under gas anesthesia by stereotaxic injection of the vasoconstrictor endothelin 1 (ET1) adjacent to the left middle cerebral artery. One, 3, 7, and 14 days after stroke, rats were assessed for neurological deficits using a standardized scoring system. Forelimb bias to the ipsilateral left side was assessed using the cylinder test, and coordinated walking was assessed with an automated ladder walk. Following behavior assessments, rats were humanely euthanized and blood and brains were collected. The effects of stroke and treatments were compared to intact sham stroke (SHAM).

Results: Peripheral oxidative stress measured by Advanced Oxidative Protein Products (AOPP) was significantly negatively correlated with T levels, similar to men. ST rats experienced the smallest neurological deficits following stroke, suggesting that

Sponsor: RO3AG049255
IRB/IACUC#: 2017-0009
NADPH oxidase (NOX1) mediates testosterone-induced neurodegeneration

Background: Parkinson’s disease (PD) has been recorded as the second most common neurological disease. Oxidative stress (OS) plays a key role in the pathogenesis of PD. Several studies have established that Parkinson’s disease (PD) is sex biased, affecting more men than women. Testosterone, a primary male sex hormone and a known oxidative stressor, has been implicated in PD. Previous studies in our lab have shown that testosterone via a non-genomic mechanism exacerbates OS damage in dopaminergic neurons. However, the mechanism by which testosterone increases OS is unknown. We found that testosterone acts through a membrane associated androgen receptor (mAR) variant – AR45 leading to the activation of proinflammatory mediators; NF-κB and COX2. NADPH Oxidase 1 (NOX 1) is a major OS generator in cells, hence a potential contributor to the pathogenesis of neurological diseases. It is possible that NOX 1 complexes with the mAR to mediate this destructive process.

Purpose: The primary objective of this study is to determine the underlying mechanism by which testosterone increases OS in dopaminergic neurons. We therefore hypothesize that in dopaminergic cells, testosterone increases oxidative stress by activating NOX 1. Ultimately, our goal is to identify pathways regulated by testosterone in dopaminergic neurons in order to provide effective pharmacological targets to enhance the treatment of PD.

Methods: We used a dopaminergic cell line (N27 cells). For an oxidative stressor, we used tert-butylhydrogen peroxide (H2O2) to induce 20% cell loss prior to testosterone (100nm) administration. NOX 1 inhibitor, Apocynin was administered before H2O2 exposure. To examine membrane associated androgen receptor and not the classical androgen receptor, we used cell impermeable DHT-BSA (500 nM) to confirm that NOX 1’s effect is through a non-genomic mechanism. Cell viability and OS were quantified using the MTT and Reduced Thiols assays respectively. To determine if NOX 1 interacts with a mAR, we immunoprecipitated the mAR and probed for NOX 1.

Results: Apocynin alone had no effect on cell viability and OS. Further, Apocynin alone, did not alter H2O2-induced cell loss, indicating that H2O2 increases OS via a non-NOX 1 mechanism. However, Apocynin blocked testosterone’s induced cell loss and OS generation suggesting that NOX 1 mediates testosterone’s damaging effects in an OS environment. Inhibition of NOX 1 also blocked DHT-BSA’s damaging effects on cell viability in an OS environment. NOX 1 protein also complexes with the mAR.

Conclusion: Testosterone-induced cell loss is mediated by a NOX1/mAR complex, indicating that NOX 1 is involved in testosterone-induced OS generation. The findings of these experiments provide a better insight into testosterone’s role in neurodegeneration and its underlying mechanism.

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IRB/IACUC#: N/A
Cocaine-induced stroke susceptibility: motor and cognitive outcomes

Purpose:

Epidemiological findings suggest that the number of young individuals suffering from stroke seems to be increasing, and one of the most common cause for such an increase is the use of illicit drugs. Prior work in our laboratory suggested that life-long cocaine intake impaired cognitive function and that short-term intake induces brain changes conferring vulnerability. In this study, we tested the hypothesis that repeated cocaine use will induce brain vulnerability to ischemic stroke.

Methods:

Fifty seven young male Sprague-Dawley rats (3 months) were injected i.p. with cocaine (10mg/kg) or saline (3 times/wk) for 4 weeks. From each treatment group, half of the rats received an ischemic stroke (transient Middle Cerebral Artery Occlusion) and the other half a sham surgery. After a one month recovery period, the rats were subjected to a behavioral battery of tests measuring balance, motor function, spatial learning and long term memory (locomotor activity, bridge walking, rotorod, and Morris water maze). Once behavioral testing was finalized the rats were euthanized and brain regions were collected for further biochemical analyses. Data were analyzed using 2- or 3-way ANOVAs followed by pairwise comparisons.

Results:

The stroke surgery resulted in decreased body weights and increased overall activity (total distance travelled and horizontal activity). Maximum performance on the rotorod was lower for the stroked rats than for the shams, and treatment with cocaine did not affect the outcome. However, during training the cocaine-treated rats had higher latencies than the controls. On the bridge walking test, the stroke surgery did not seem to affect performance, however the cocaine-treated stroke rats performed the worst. The stroked rats took longer path length and latencies to reach the platform, and cocaine seem to exacerbate the impairment, more specifically at the end of training and during retention.

Conclusions:

While preliminary, these results suggest that cocaine-treated rats were more vulnerable to stroke than the saline-treated ones but exhibiting exacerbated impairments on balance and spatial learning and memory. Studies to identify the underlying mechanisms of this vulnerability are underway.

Sponsor: Intramural grant UNTHSC RI10014
IRB/IACUC#: 2016-0022
Hormone treatments reverse stroke-associated declines in cognitive function in a rat model of menopause

Purpose

This study addresses the critical questions important to the future of hormone therapy. The purpose of this study was to provide information on how different durations of hormone deprivation can alter the responsiveness of the brain to ischemic injuries and hormonal therapies. Ultimately, these studies will identify a window of opportunity for treatment with hormones preventing brain dysfunction associated with menopause.

Methods

Eighty-two Sprague-Dawley retired breeder females rats were ovariectomized (ovx). Twelve or two weeks post-surgery, the rats were implanted with hormone pellets containing cholesterol (vehicle), estrogen (E2) or progesterone (P4), which were replaced every 2 weeks. Two weeks post implantation, the rats received either a sham or ischemic stroke (transient Middle Cerebral Artery Occlusion) surgery. After a one week recovery period, the rats were subjected to a behavioral battery of tests measuring affective (plus maze), motor (rotorod) and cognitive (Morris water maze) function. The rats were then euthanized and brain regions were collected for further biochemical analyses. Data were analyzed using 2- or 3-way ANOVAs followed by pairwise comparisons.

Results

Treatment with E2 or P4 decreased the time spent in the open arms in both 2 and 12 weeks post-ovx groups. There was no effect of stroke or hormone treatment on the rotorod. For spatial learning and memory, stroke impaired the rats in their ability to learn and retain the location of the platform and impairments were worst in the 12-weeks post-ovx group. E2 and P4 treatment improved performance of the stroke rats in both 2 and 12-weeks post-ovx groups.

Conclusions

These data suggest that the outcome of stroke is worst as a function of time post-ovx, especially on spatial learning and memory. Hormonal treatment with E2 and P4 were successful in reversing the deleterious effects of stroke on cognitive function. Further studies to identify the mechanisms underlying these observations are underway.

Sponsor: P01 AG027956
IRB/IACUC#: 2014 15-49
Administration of 5-methoxyindole-2-carboxylic acid that potentially targets mitochondrial dihydrolipoamide dehydrogenase confers cerebral preconditioning against ischemic stroke injury

Purpose: The purpose of this study was to investigate a possible role of mitochondrial dihydrolipoamide dehydrogenase (DLDH) as a chemical preconditioning target for neuroprotection against ischemic injury.

Methods: We used 5-methoxyindole-2-carboxylic acid (MICA), a reportedly reversible DLDH inhibitor, as the preconditioning agent and administered MICA to rats mainly via dietary intake. Upon completion of 4 week’s MICA treatment, rats underwent 1 h transient ischemia and 24 h reperfusion followed by tissue collection.

Results: Our results show that MICA protected the brain against ischemic stroke injury as the infarction volume of the brain from the MICA-treated group was significantly smaller than that from the control group. Data were then collected without or with stroke surgery following MICA feeding. It was found that in the absence of stroke following MICA feeding, DLDH activity was lower in the MICA treated group than in the control group, and this decreased activity could be partly due to DLDH protein sulfenation. Moreover, DLDH inhibition by MICA was also found to upregulate the expression of NAD(P)H-ubiquinone oxidoreductase 1 (NQO1) via the Nrf2 signaling pathway. In the presence of stroke following MICA feeding, decreased DLDH activity and increased Nrf2 signaling were also observed along with increased NQO1 activity, decreased oxidative stress, decreased cell death, and increased mitochondrial ATP output. We also found that MICA had a delayed preconditioning effect four weeks post MICA treatment.

Conclusion: Our study indicates that administration of MICA confers chemical preconditioning and neuroprotection against ischemic stroke injury.

Sponsor: NIH
IRB/IACUC#: 2014-15-32-A05
Histone deacetylase signaling plays a critical role in age-related decrease in adult neurogenesis

Aging is associated with a striking increase in the incidence of stroke and neurodegenerative diseases, both of which are major causes of disability among those age 70 years and older in the United States. Adult neural stem/progenitor cells (NSCs) hold great promise for brain repair due to their unique location within the central nervous system, which continues through the life span. However, neurogenesis is significantly declined with aging.

Purpose: the underlying mechanisms remain largely unexplored.

Methods: HDAC expression in the young adult and aged brain was determined by immunohistochemistry. And then the young adult and old rats are administrated with histone deacetylases (HDACs) inhibitor by intraperitoneally and then immunohistochemistry test was performed. Results: First, we found that HDACs I and II were expressed in the NSCs in the subventricular zone (SVZ) and the subgranular zone (SGZ) of hippocampus in normal adult rat brain using immunohistochemistry. Second, the expression level of HDACs in the SVZ and SGZ was significantly altered in aged brain compared with young adult brain. In addition, the number of NSCs in aged brain was significantly increased after administration of HDAC inhibitor.

Conclusion: Our data suggest that HDAC signaling may be an important factor in determining the neurogenesis in aged brain.

Sponsor: N/A
IRB/IACUC#: IACUC-2017-0052
Pulmonary thromboembolism. A clinical case with misleading presentation

Background

Pulmonary embolism is a common and sometimes fatal disease. And despite its high incidence, the diagnosis continues to be very challenging and easily missed.

Case Presentation

We present a case of a 51 year old female with no past medical or surgical history who presented with complaints of shortness of breath and fatigue. Her only complaint was heavy menstrual flow lasting more than 7 days. On admission, physical exam was unremarkable. Vitals were stable. Patient was in no acute distress. Respiratory exam revealed clear lungs bilaterally. Examinations of her legs were normal. Negative Homans sign. GU exam showed patient was actively menstruating.

Levels of serum electrolytes, glucose, BUN and creatinine were normal. CBC showed a hemoglobin of 6.7, hematocrit of 23.1 and MCV of 60.3. Platelet count was normal at 325. Iron studies obtained showed an iron level of 12, TIBC of 436, % saturation of 2.75 and ferritin level of 7. An ECG showed a regular sinus rhythm. Chest Xray was normal. Patient was diagnosed with Symptomatic anemia. Type and screen was ordered and patient was transfused with 2 units of PRBC.

Wells score was calculated to be 0. However, PERC rule was applied, showed a score of 1 based on age > 50. Thereby necessitating further evaluation. A D-Dimer was obtained and found to be >5000. CTA showed an extensive bilateral lobar and segmental pulmonary thromboembolism, and possible right heart strain. The patient received standard anticoagulation treatment with unfractionated heparin.

Conclusion

Pulmonary embolism is a frequent cause of death in the United States. However, the clinical picture of pulmonary embolism is variable and most patients do not present with the classic triad of pleuritic chest pain, dyspnea, and hemoptysis.

The Clinician should always remember to use the PERC rule in any patient that present with any one of these classic triad. And remember that a D-dimer level still remains very important to rule out PE.

Sponsor: N/A
IRB/IACUC#: MCFW-IRB
Effect of Nicotine Consumption in Auto-Brewery Syndrome

Purpose: Auto-Brewery Syndrome (ABS) is a rare condition defined by a proliferation of yeast species in the gut, where they enter the bloodstream. Patients typically show signs of intoxication upon carbohydrate ingestion as a result of yeast fermentation. A literature review reveals several cases of patients with diagnosed ABS who were admitted to the hospital for psychosis and agitation. In addition to ABS, patients often present with several comorbidities, including Chronic Traumatic Encephalopathy (CTE) and a history of e-cigarette or tobacco consumption. Given the temporal relationship between nicotine consumption and the onset of psychotic episodes in these patients, there may be a link between nicotine consumption and worsening psychosis in patients with CTE and ABS.

Question/hypothesis: Could nicotine consumption exacerbate Auto-Brewery Syndrome to induce psychotic episodes in the setting of Chronic Traumatic Encephalopathy?

Methods: An English literature review of case reports involving patients who are smokers with concurrent ABS and CTE and an English literature review on the effects of nicotine in the body.

Results: The literature suggests a connection between nicotine consumption and increased catecholamine levels, which can increase glucose production and blood glucose levels. The proposed mechanism involves activation of the nicotinic acetylcholine receptors in the adrenal medulla, which increase the production and release of catecholamines, namely epinephrine. Epinephrine then binds B2 receptors on the liver and skeletal muscles, upregulating glucose production and release. The glucose may then be fermented by yeast in the bloodstream, resulting in alcohol toxicity and/or psychotic episodes.

Conclusion: Our review shows that patients experienced an increase in psychotic episodes while staying at a psychiatric hospital where they were provided with cigarettes and produced elevated BAC measurements during these events. The mechanism by which nicotine increases glucose production in the body led us to believe that these patients were experiencing ABS exacerbations secondary to nicotine consumption, inducing psychotic events in the CTE setting.

Sponsor: N/A
IRB/IACUC#: N/A
The Potential Role of E-Cigarettes In Diffuse Alveolar Damage

Purpose: The prevalence of e-cigarette usage has increased in non-smokers and those planning to quit smoking. Although the potential long term adverse effects have not been studied in humans, studies have shown that certain components of e-cigarette fluid may lead to the release of cytotoxic components implicated in the pathogenesis of diffuse alveolar damage (DAD), a histopathological diagnosis that is commonly associated with acute respiratory distress syndrome (ARDS). This literature review describes the potential association between e-cigarettes and diffuse alveolar damage while making reference to relevant associated studies.

Methods: An English literature review of studies that examine the potential cytotoxic effects of E-cigarette fluid components in relation to the pathophysiology of diffuse alveolar damage.

Results: To date, no longitudinal studies have been performed on humans to show the toxicity of e-cigarette vapor on the human lung. However, studies have shown different mechanisms by which the compounds in e-cigarette vapor lead to the destruction of alveolar epithelial cells in-vitro.

The major component of e-cigarette vapor, propylene glycol, has been shown by in-vitro studies to be cytotoxic to alveolar type II epithelial cells. Glycerol, another component of e-cigarettes, was also found to be cytotoxic in a dose-dependent pattern. Moreover, lactate dehydrogenase, a common byproduct of cell death, was found elevated in alveolar cells exposed to e-cigarette vapor when compared to alveolar cell controls exposed to clean air, suggestive of cell death.

Interleukin-6 (IL-6), a proinflammatory cytokine, was found to be elevated in a dose dependent pattern after young healthy non-smokers hTBE cells (human tracheobronchial epithelial cells) were exposed to e-cigarette fluid. Furthermore, there was an increase in fibroblast growth factor (FGF) in alveolar cells, which is also part of the pathogenesis of DAD.

Conclusion: Diffuse alveolar damage is a life-threatening condition with a high mortality rate. The evidence of adverse effects demonstrated by the in-vitro studies described above suggests an association between e-cigarette use and diffuse alveolar damage. Just as studies were able to reveal the harmful effects of tobacco products in the past, this literature review introduces a new avenue of investigation to assess the long-term effects of e-cigarettes on humans.

Sponsor: N/A
IRB/IACUC#: N/A
The Radiographic Prepatellar Fat Thickness Ratio Correlates with Infection Risk following Total Knee Arthroplasty

1. Purpose

Obesity has been associated with complications following a total knee arthroplasty (TKA). Surgical Site Infection (SSI) following TKA is one of the feared complications as it increases revision rates, costs, and stress to the patient. There is conflicting evidence in the literature regarding BMI and risk of infection after TKA and some studies have suggested that site-specific fat distribution may be a better metric for determining risk of postoperative infections. Here we investigate the correlation of soft tissue distribution about the knee to surgical site infection following TKA.

2. Methods

We retrospectively review 572 patients who underwent primary TKA at a single institution from 2006 to 2010. We introduce the Prepatellar Fat Thickness Ratio (PFTR) as a radiographic means to quantitatively assess fat distribution about the knee and evaluate this measurement’s ability to assess the risk of developing a SSI following TKA.

3. Results

The PFTR was shown to be a better predictor of SSI than BMI in both the univariate (p=0.05) and multivariate (p=0.01) analyses.

4. Conclusions

While BMI cannot fully account for variations in adipose distribution, the PFTR may account for this variability and may be a helpful tool for assessing a patient’s preoperative risk of SSI after TKA.

Sponsor: N/A
IRB/IACUC#: 2015-163
Postural control and use of eye movements differ during quiet standing in Autism Spectrum Disorder and Typical Development

PURPOSE: Individuals with Autism Spectrum Disorder (ASD) have clinically-significant difficulty with postural stability and motor coordination. However, few studies quantitatively examine differences in postural stability and eye movement between ASD and typical development (TD). Individuals with ASD have atypical eye movements, and emerging evidence suggests that they also have difficulty using vision to support postural control. This study aimed to quantify differences in eye movement and postural stability between individuals with ASD and TD.

METHODS: 18 individuals with ASD ($M_{age} = 15.3$) and 23 TD ($M_{age} = 14.3$) participated in this study. Participants stood on a force plate while wearing eye-tracking glasses. The force plate monitored their center of pressure, a common metric used to assess balance and stability. The eye-tracking glasses monitored their fixation and saccadic eye movements. Participants completed a quiet standing task with three conditions: eyes open (EO), eyes closed (EC), and EO while wearing a translucent dome on the head, obscuring visual context (Dome). Each condition lasted 30 seconds, and participants were monitored for compliance by a member of the research team.

RESULTS: Participants in the ASD group had greater overall postural instability than the TD group across all conditions. Notable differences also occurred between the groups for anterior-Posterior sway and sway in the EO condition. The two groups also differed in proportion of fixations versus saccadic eye movements used to support postural stability.

CONCLUSIONS: These data suggest that the specific profile of postural instability and contributing eye movements differs between ASD and TD. The ASD group had markedly increased instability when visual context was eliminated (EC) or obscured (Dome), suggesting an important influence of visual information and potential failure to engage in sensory reweighting. Sensory reweighting is critical function, increasing flexibility in the strategies a person uses to maintain balance in situations where one dominant source of sensory input (e.g., vision) is unreliable or unavailable. Data collection is ongoing, and additional studies are necessary to investigate the mechanisms responsible for postural instability in ASD.

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IRB/IACUC#: 2015-010
Surface Plasmon Assisted Microscope (SPAM)

The purpose of this research was to construct the instrument to image 10-20 nm thick layer of cells such as membrane lipids, membrane receptors and other structures proximal to basal membranes. Until now this task was best achieved by Total Internal Reflection Microscopy (TIRF).

Here we demonstrate an alternative method which has number of advantages over TIRF. The materials required for constructing such an instrument include inverted microscope, a high refractive index coverslip covered with 50 nm thick layer of gold and an optical fiber coupled laser.

A sample is placed on a high refractive index coverslip coated with a metal instead of glass and is illuminated by the laser from the top (through aqueous medium). Fluorophores that are close to the metal surface induce surface plasmons in the metal film. Fluorescence from fluorophores near the metal surface couple with surface plasmons allowing them to penetrate the metal surface and emerge at a Surface Plasmon Coupled Emission (SPCE) angle. Fluorescence is collected by a high NA objective and imaged by EMCCD or converted to a signal by avalanche photodiode fed by a single mode optical fiber inserted in the conjugate image plane of the objective.

We compared images of cell monolayer of astrocytes transfected with GFP obtained by SPAM with image obtained by TIRF. We think that SPAM image was clearer than TIRF image because: 1. Thickness of the detection layer was reduced in comparison with TIRF because metal quenched fluorophores at a close proximity (below 10 nm) to a surface; 2. The system avoided complications of through-the-objective TIRF associated with shared excitation and emission light path; 3. The microscope had excellent background rejection because all far-field radiation is reflected by the mirror-like metal layer.

Sponsor: N/A
IRB/IACUC#: N/A
Incorporation of pharmacy personnel into medical mission trips: Benefits of an interprofessional team

There is a multitude of literature discussing the benefits of having pharmacy services incorporated into the medical mission team, however very few articles discuss in detail how pharmacists provide those services. The UNTHSC Christian Medical Association organizes an annual trip to various countries in Central America and has recently started incorporating pharmacists. The objective of this research was to review the literature within the last decade on the contribution of a pharmacist on the medical mission team. A secondary aim was to identify specific areas for consideration, such as medication acquisition, formulary development and pediatric dosing.

A review of the literature was conducted identifying articles by searching PubMed, Scopus and Academic Search Complete, using the keywords ‘pharmacy’, ‘mission trips’, ‘medical missions’, ‘formulary’, and ‘religious missions.’ Articles that were published between 2007 and 2017 were included in the analysis. A summary was provided based on eight subtopics: acquiring medications; formulary development; work flow; transportation; packaging, labeling and medication setup; medication data collection; counseling; and pediatrics. A template was developed reflecting medical mission trip workflow.

The search yielded a total of 10 articles for review. Findings revealed that medication acquisition and formulary development are key pre-trip roles for pharmacists. If medication is being brought outside the country where the trip is taking place, pharmacists should research the foreign country’s policies beforehand to ensure there are no issues with customs during travel. Counseling and work flow were the most common roles in terms of impact. Packaging and labeling improved efficiency for patients when customized to their language preference. Few studies thoroughly examined pediatric dosing, and none of the studies highlighted the pharmacist’s role in pediatric dosing.

Previous literature has shown that pharmacy services are beneficial, but developing more standardized methods of how to utilize pharmacy services will help increase pharmacist contributions on mission trips. Since pharmacist involvement is a newer idea, there are a lack of empirical studies to measure the success of pharmacist involvement. More research using randomized control trials or specific outcome measures would benefit the existing body of literature. An opportunity exists for pharmacists to effectively contribute on an interprofessional team.

Sponsor: N/A
IRB/IACUC#: N/A
Deconstructing Dogma: Non-Operative Management of Small Bowel Obstruction in the Virgin Abdomen

Purpose: Management of small bowel obstruction (SBO) has become more conservative, especially in those patients with previous abdominal surgery (PAS). However, surgical dogma continues to recommend operative exploration for SBO with no PAS. With the increased use of CT imaging resulting in more SBO diagnoses, it is important to reevaluate the role of mandatory operative exploration. Gastrografin administration decreases the need for operative exploration and may be an option for SBO without PAS. We hypothesized that the use of GG for SBO without PAS will be equally effective in reducing the operative exploration rate compared to that for SBO with PAS.

Methods: A post-hoc analysis of prospectively collected data was conducted for patients with SBO from February 2015 through December 2016. Patients < 18 years, pregnant patients and patients with evidence of hypotension, bowel strangulation, peritonitis, closed loop obstruction or pneumatosis intestinalis were excluded. The primary outcome was operative exploration rate for SBO with or without PAS. Rate adjustment was accomplished through multivariate logistic regression.

Results: Overall, 601 patients with SBO were included in the study, 500 with PAS and 101 patients without PAS. The two groups were similar except for age, gender, prior abdominal surgery including colon surgery, prior SBO admission and history of cancer. Multivariate analysis showed that PAS (OR = 0.47, p=0.03) and the use of GG (OR = 0.11, p

Conclusion: Patients with and without PAS who received GG had lower rates of operative exploration for SBO compared to those that did not receive GG. Patients with a diagnosis of SBO without PAS should be considered for the non-operative management approach using GG.

Sponsor: N/A
IRB/IACUC#: JPS-060115.001ex (FWA 00011753)
Patient Surveys Referring to Urine Sample Collection Methods: A Quality Improvement Study at Cook Children’s Urgent Care Centers

Background: Urinary Tract Infections (UTIs) are a common problem amongst Pediatric Urgent Care Centers (UCCs) and are usually the result of various bacterial species. While many factors are considered when diagnosing a UTI, the urinalysis remains the most important screening tool and a urine culture gives diagnostic confirmation. The sensitivity and reliability of a urinalysis is affected by many factors including the urine collection method. A previous retrospective study found that Cook Children’s UCCs had high rates of urine contamination (defined as

Hypothesis: We hypothesize that Cook Children’s midstream urine collection policy is not being followed/enforced.

Methods: A quality improvement (QI) study was designed and conducted at Cook Children’s Pediatric UCC in Fort Worth. The Fort Worth site was chosen because of its historically high patient volume. A survey was developed with questions that modeled Cook Children’s midstream urine collection policy. Surveys were given verbally to patients who gave a urine sample and met the inclusion criteria: potty trained. Families could follow along with a provided copy of the survey. The data were collected over a four-week period, placed into REDCap, and analyzed according to survey questions.

Results: Of those surveyed (n=24) less than 10% received gloves; 35% of female patients and 66% of uncircumcised male patients were properly instructed to clean their genitalia. Midstream urine collection instructions were given to 26% of patients, and more than 50% of patients claimed to not collect urine midstream.

Conclusions: The results from this preliminary study demonstrate that Cook Children’s midstream urine collection policy is not properly followed by the UCC staff. There is evidence that rates of urine contamination and improper UTI diagnosis are high. As such, future interventions will focus on educating the UCC staff on Cook Children’s policy and employing a check off to make sure all members of the staff are properly trained on giving patient instructions for midstream urine collection.

Sponsor: N/A

IRB/IAUC#: CCHCS-IRB
Subcutaneous Depth in Kidney Transplantation: Indication for Negative Pressure Wound Vacuum Therapy?

Purpose: Wound complications after kidney transplant (KTx) consume valuable resources, including prolonged hospital stays and increased costs. Risk factors include immunosuppression exposure, diabetes, and obesity as indexed by body mass index (BMI). However, BMI is not an accurate surrogate of body habitus. In this study, we sought to determine the effect of subcutaneous depth (SQD) on KTx outcomes, specifically wound complications.

Methods: We measured SQD in 97 KTx only (79 cadaveric;18 living donor) only over 18 months. The mean age of the recipients (56M:41F) was 48 years, with an average BMI 27.8. SQD was measured from the midpoint of the lateral portion of the incision and measured the distance from the fascia to the skin edge, to the closest 0.5cm. Data analyzed included presence of diabetes, hypertension, PRA, pretransplant dialysis, prior transplant, and induction therapy. Post transplant complications analyzed included wound infection, dehiscence, lymphocele, renal artery thrombosis/stenosis, urine leak, ureteral stenosis and need for vacuum assisted closure therapy.

Results: The average SQD of our recipients was 2.9cm. Patients with a SQD >2.5cm were more likely to require wound vac therapy (average length of therapy, 46.6 days) compared to those with a SQD ≤ 2.5cm, SQD >2.5cm was still associated with a higher likelihood of requiring a wound vac (odds ratio 3.4).

Conclusions: In summary, SQD >2.5cm is an independent risk factor for requiring negative pressure vacuum therapy. This is a simple intraoperative identifier which should stratify those at risk for later intervention.

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IRB/IACUC#: BSW-IRB 009-261
1810 - Poster

Classification: TCOM DO Student (2nd Year)

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Health Status, Healthy Lifestyle Practices, and Attitudes toward Lifestyle Counseling among Medical Students at the Osteopathic Medical School and Allopathic Medical School in DFW: A Cross-Sectional Analysis

Purpose: By 2020, the World Health Organization predicts that 63% of all worldwide diseases and deaths will be associated with poor lifestyle choices which individuals, families, or groups make every day. It is imperative that health care providers adopt and demonstrate evidence-based and patient-centered competent approaches to improving patients’ lifestyle habits for health promotion, disease prevention, and therapeutic effects. Since medical students are the future of medicine, it is important to investigate their health status, health habits practice, and readiness to engage in lifestyle counseling. Further, it is interesting to investigate if any difference exists between osteopathic and allopathic medical students.

Methods: A survey is the key instrument in this cross-sectional study to assess the health status, health habits practice, and attitudes towards engagement in lifestyle counseling among medical students. The survey contains questionnaires, which are in the multiple choice and closed-ended formats. The survey will be sent out via email separately to each TCOM class and each UT Southwestern (UTSW) class. The survey being sent out to TCOM is through Qualtrics and the survey for UTSW is through REDCap.

Data: Data is in the process of being collected through Qualtrics for TCOM and REDCap for UTSW. All data at UTSW will be sent to the researcher at TCOM and analyzed. The analysis will be conducted using Statistical Analysis System version 9.4.

Hypotheses: The primary hypothesis is that there will be a relationship between health status, health lifestyle practice, and attitude to engage in lifestyle counseling and years spent in medical education. The secondary hypothesis is that there will be a difference in health status, healthy lifestyle practice, and attitude to engage in lifestyle counseling among medical students in different levels of medical education. The tertiary hypothesis is that there will be a difference in health status, healthy lifestyle practice, and attitude to engage in lifestyle counseling among osteopathic medical students and allopathic medical students.

Sponsor: N/A

IRB/IACUC#: 2017-118/UTSW-112017-044
How bamboo has shaped the anatomy and physiology of Hapalemur

Purpose

Hapalemurspps. and Prolemursimus (bamboo lemurs) stand out among the relatively homogeneous lemurids because they are bamboo feeders and vertical climbers and leapers. This unique diet presents equally unique challenges, like its verticality, toughness, and toxicity. The bamboo lemurs share the generalized anatomy of the other lemurids, but also display some well-documented adaptations in their limb proportions to overcome the problems presented by bamboo. Soft tissue adaptations, however, remain largely unexplored. Here we begin to explore possible soft tissue adaptations in Hapalemur griseus. Based on the available anatomical and physiological data obtained from other Hapalemur and Prolemur species, we predict that H. griseus will have differences in hindlimb morphology when compared to other lemurids. We further predict that H. griseus will have more hindlimb muscle mass and will amplify muscle mass differences with increased type II muscle fibers.

Methods

We compared regional muscle mass, relative to total muscle mass, in mainland African, Malagasy, and Asian prosimians and a tree shrew (n = 11). Raw regional muscle mass values (e.g., hindlimb and sural) were divided by total muscle mass for a particular species to compare relative muscle mass. We then used immunohistochemistry to evaluate the fiber profile (the relative amount of type I/type II fibers) of muscles of significance, based on the results of the comparison of muscle masses.

Results

Relative hindlimb muscle mass in H. griseus is no different than other lemurids (p = 0.26). However, relative sural muscle mass is significantly heavier (p < 0.01) in H. griseus than other lemurids. When the fiber profiles of primary foot plantar flexors were evaluated, the soleus muscle of H. griseus displayed a higher amount of type II (fast) fibers than any other species.

Conclusions

These findings indicate that although H. griseus shares some generalized lemurid morphology, its diet of bamboo has pushed this generalized lemurid to an anatomical extreme. We suspect that based on the diameter of the bamboo stalk and the bamboo lemurs body size, bamboo lemurs may be leaping in a unique fashion that does not easily fit with small-bodied “foot-powered” leapers or large-bodied “hip-powered” leapers. Although the results are preliminary, we suspect additional bamboo-specific adaptations in their anatomy and physiology will be uncovered with further examination into the anatomy of the bamboo lemurs.

Sponsor: National Science Foundation, Grant number:1440624
IRB/IACUC#: N/A
Contamination Rates in Urine Collection at Cook Children’s Pediatric Urgent Care Centers

Background: Over $180 million in health care costs are spent annually on pediatric urinary tract infections (UTIs). Pediatric UTI symptoms are often non-specific causing physicians to rely on the results of a urine dip stick to assess appropriate follow up and treatment. Improper urine collections can result in bacterial contaminations and can mask true urinary tract infections. This would lead to inaccurate diagnosis, unnecessary treatment, and/or obtaining additional specimens, all adding to the burden of increased costs and patient/parental anxiety.

Hypothesis: Cook Children’s Urgent Care Clinics (UCCs) have significant contamination rates from patients who gave mid-stream urine.

Methods: Data collection consisted of a six-week retrospective chart review on patients with suspected UTI at each UCC location. Included in this study were patients five years and older and able to collect a mid-stream urine. Data was placed into Red Cap database. Contamination was defined as culture results = 12 yrs) on the assumption that adult supervision was needed in the former group. Contamination rates were then calculated for age, gender, and UCC location.

Results: Of the 258 charts reviewed, 202 met the criteria for this study. The sample size was significantly smaller for males (13%) than females (87%). Total contamination rate was 30% (p=). Based on age, contamination rates showed 54% for 5-11 yrs and 46% for 12 yrs and older (p=0.0069). Females were more likely than males to have contamination, 33% vs 11.5%, respectively (p=0.026). There was no significant relationship between UCC location and contamination (p=0.52). Small, moderate, and large amounts of leukocyte esterase were associated with infection (p=0.0006), however, trace results were not.

Conclusions: The results from this preliminary study reinforce significant urine collection contamination rates. Chart reviews will be completed to provide a more robust sample size, but steps need to be taken to determine what is causing this high rate. To elucidate these variable(s), surveys (patient/family and provider) will be obtained to assess collection methods: how the urine is collected (parent/patient perspective), how it is thought to be collected in the clinic (provider perspective), and financial burdens to the family and institution (administrative perspective).

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
POST-OP BLEEDING IN A PATIENT WITH NOONAN SYNDROME AND FACTOR XIII DEFICIENCY: A CASE STUDY

Background: Factor XIII, also known as fibrin stabilizing factor, strengthens the final stages of hemostasis. It plays a pivotal role in angiogenesis, maintenance of pregnancy, wound healing, bone metabolism and cardio protection. A deficiency in this factor is inherited in an autosomal recessive fashion or an antibody against the factor can be developed. Noonan syndrome is a common genetic abnormality that is characterized by webbed neck, short stature, characteristic facies, congenital heart defects, and developmental delay. It is inherited in an autosomal dominant fashion. Commonly, patients with this disease present with a proclivity for bleeding diathesis due to platelet and coagulation factor abnormalities.

Case Information: We present a 13-year old boy with known Noonan syndrome who experienced profuse bleeding from the left ear and a large hematoma formation after an otologic procedure. Although Noonan patients are known to experience bleeding complications, our patient had undergone various surgical procedures without prior hemorrhagic events. Due to retained ear tubes and chronic suppurrative otitis media, the patient developed conductive hearing loss and was recommended to receive surgical intervention. The patient presented the following day to the emergency department with bleeding from the left ear and hematoma of the left side of his face and neck. He was discharged after bleeding was stopped; but once home, the bleeding started again, and he was re-admitted for an exploratory exam under general anesthesia. Diffuse oozing was discovered, and a platelet transfusion was provided to stop the bleeding. A bleeding disorder workup was sent including a factor XIII activity assay. Preliminary coagulation tests proved normal, however factor XIII deficiency was confirmed.

Conclusions: This is the first described case of factor XIII deficiency presenting in a patient with Noonan syndrome. Noonan patients have a proclivity for bleeding diathesis, but much more commonly due to other factor and platelet abnormalities. Noonan syndrome is common enough that many clinicians and surgeons will see these patients in their practice. It is important to be aware of the common bleeding disorders associated with Noonan syndrome, but also to be aware that they can have other rare bleeding disorders despite normal basic coagulation tests.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Severe Hypercholesterolemia in Two Children

Background: Extreme elevations of low-density lipoprotein cholesterol (LDL-C) levels are generally consistent with genetic mutations affecting lipid or lipoprotein metabolism, as seen in familial hypercholesterolemia (FH). A detailed family history, medical history, and routine labs are key in determining the underlying cause to support appropriate clinical decision-making. We report two children with severe hypercholesterolemia and discuss evaluation and treatment.

Case 1: A 2-yr-old Hispanic female presented for possible FH after routine lab test reported a severely elevated LDL-C of 370 mg/dL. The medical and family histories were unremarkable. Additional tests were ordered to rule out 2nd causes of hypercholesterolemia; her free T4 was low and her TSH elevated. Upon further questioning, the mother stated that the child was diagnosed with congenital hypothyroidism at birth and was started on thyroid hormone, but had been without it for 5 mos. Within 6 weeks of resuming levothyroxine, LDL-C was normal (78 mg/dL).

Case 2: A 16-yr-old male was referred for evaluation after a cholesterol-screening test, performed by his PCP, reported an LDL-C of 213 mg/dL. His past medical history was unremarkable and he denied the use of medications. Both parents denied any significant family history. Additional studies revealed a low free T4 and an elevated TSH. He was found to have thyroid antibodies, consistent with the clinical impression of Hashimoto’s disease. Upon treatment with levothyroxine, thyroid function studies and LDL-C were normal (106 mg/dL).

Summary: FH is a common genetic mutation that is frequently encountered in primary care. Although severe elevations in LDL-C are generally consistent with genetic mutations in lipid or lipoprotein metabolism, secondary causes must be considered. Both patients presented for evaluation of FH but were diagnosed with hypothyroidism. The dramatic decline of their LDL-C values within 6 weeks of treatment with levothyroxine emphasizes the importance of ruling out secondary causes of hypercholesterolemia. Thyroid dysfunction can lead to alteration of lipid metabolism due to the effects of low thyroid hormone on HMG-CoA reductase, LDL receptor expression, and high-density lipoprotein.

Conclusions: While severe elevations of LDL-C can be caused by genetic mutations affecting lipid and lipoprotein metabolism, secondary causes of hypercholesterolemia should be excluded prior to counseling, genetic testing, and implementation of lipid-lowering therapy.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Congenital and Hematologic Abnormalities in an Infant with a Novel GATA1 Mutation: A Case Study

Background: The GATA genes encode a family of transcription factors that are important for the development and differentiation of different cell lines. GATA1 is required for the development of cells of myeloid lineage and has been implicated in many diseases including transient myeloproliferative disorder, acute megakaryoblastic leukemia, and Diamond Blackfan anemia. This case study explores the clinical presentation of a novel GATA1 mutation.

Case Presentation: A Caucasian male was born at 36 weeks gestation with a prenatal history significant for pericardial effusion, restrictive patent ductus arteriosus and polyhydramnios. Due to these anomalies, amniocentesis was performed which revealed normal chromosomes. At birth, he presented with decreased tone and respiratory distress so he was placed on continuous positive airway pressure and was transferred to Cook Children’s Medical Center. On physical exam, he had micropenis, hypospadias, bilateral clubfoot and blueberry muffin spots on the abdomen. Persistent leukocytosis, anemia and thrombocytopenia during the first month of life prompted consideration of a primary hematologic condition. A bone marrow exam was performed which showed a small increase in blasts, a significant decrease in erythroid precursors and few megakaryocytes. Subsequently whole exome sequencing (sent during the birth hospitalization) found the patient to be hemizygous for variant p.R307C in exon 6 of the GATA1 gene – a previously unreported mutation. The patient has been free from transfusions since 3 months of age although mild hemolytic anemia and leukocytosis have persisted. Currently he is being monitored for changes in blood counts and developmental milestones.

Conclusion: The patient’s congenital anomalies and hematologic abnormalities have not been explained by another cause. His bone marrow has been sent to a research lab in Boston for functional analysis of the mutation. Additionally, the missense mutation discovered in sequencing has not been reported in the medical literature, but a mutation of the same exon of GATA1 has been previously described. The phenotype similarities between these two patients suggest that the congenital and blood anomalies are related to the missense mutation in exon 6 of the GATA1 gene. It is unclear why the mutation seems to affect mature red blood cells but not erythropoiesis. Work is ongoing to identify which targets are being modified by this mutation and how those changes impact phenotype.

Sponsor: Pediatric Research Program

IRB/IACUC#: CCHCS-IRB
Are Activity Limitations Related to Mental Health in Veterans Aged 25 and Older?

Purpose: Many veterans face difficulties such as physical limitations and mental health disorders, but little is known about how these are related within the veteran population. This study will examine the association between activity limitations and mental health in veterans aged 25 and older.

Methods: This cross-sectional analysis used 2015 BRFSS data for veterans aged 25 and older from Oklahoma, Virginia, and Washington. Multiple logistic regression analysis was used to assess the relationship between mental health and activity limitations after controlling for psychosocial and demographic variables.

Results: About one-fourth of veterans aged 25 and older reported having less than 30 days of good mental health in the past month (19-23%), and similar amounts reported having serious difficulty walking or climbing stairs (17-28%). After controlling for lifestyle and demographic factors, mental health was inversely related to activity limitations and to chronic health conditions in all three states with moderate to high effect sizes.

Conclusion: These findings indicate there is a significant relationship between activity limitations, chronic health conditions, and mental health among veterans 25 years and older. Limitations of this study include the low prevalence of female veterans which made it difficult to assess gender differences. Due to the significant relationship, it is recommended that primary care practitioners screen for activity limitations, chronic health conditions, and poor mental health if a veteran presents with any of these, and then educate and provide referral services as necessary.

Sponsor: N/A
IRB/IACUC#: 2017-070
A Case of Osteosarcoma in Concurrent Sickle Cell Disease

Background:

Osteosarcoma is an aggressive bone cancer with a poor prognosis. When this disease is coupled with a concurrent diagnosis of Sickle Cell Disease (SCD), very careful management of the treatment is necessary, due to complications that may arise. This case study will explore some of the complications that were faced in a patient with these two diseases.

Case Information:

An 11-year-old male with SCD presented to the hospital with leg pain. He was mistakenly believed to have osteomyelitis, a known complication of SCD. Imaging supported this initial diagnosis but further evaluation was ordered. A biopsy of the proximal tibia showed pleomorphic malignant cells and malignant osteoid, confirming a diagnosis of osteosarcoma. Treatment following the Children’s Oncology Group Protocol: AOST0331 was initiated. This protocol includes 29 weeks of chemotherapy consisting of alternating Methotrexate (MTX) once a week for two weeks, followed by Doxorubicin/Cisplatin one week. This is repeated until week 10, when a surgical resection of the tumor is performed, followed by 17 more weeks of chemotherapy. During treatment, several incidents that are attributable to complications of SCD occurred. Two instances of delayed MTX clearance and the formation of two intra-cardiac thrombi were the most troubling of these complications. The patient remained in the hospital during the prolonged MTX clearance, and was monitored closely until clearance was achieved. The patient also received tPA and Lovenox to dissolve the intra-cardiac thrombus and reduce the likelihood of the formation of another thrombus.

Conclusions:

SCD with a diagnosis of osteosarcoma presents unique challenges to a physician. SCD induces a hypercoagulable state and often leads to end-organ damage, and osteosarcoma is a cancer that must be dealt with aggressively to achieve remission. A diagnosis of osteosarcoma in a patient who already has SCD has the potential to be masked by the complications of SCD. Osteosarcoma must be considered a differential in someone who presents with bone pain, even if they are already known to have SCD. Once a diagnosis of osteosarcoma is made, the implications of the concurrent diagnosis of SCD requires that physicians very carefully consider the possibilities of severe complications that may arise. Managing physicians must have awareness of the effects chemotherapy can have on an individual that is both in a hypercoagulable state and may also have end-organ damage.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Analysis of the UNTHSC Teen Clinic

Background: The UNTHSC Teen Clinic was established in June 2015 by Dr. Priya Bui as a result of her experiences working with teens in the UNTHSC pediatric clinic. The clinic is run ½ day per week by Dr. Bui and PA Lauren Dobbs. Typical visits include taking a thorough history and physical, screening for psychiatric problems, running special labs (for STIs, lipids, etc.) when indicated, and conducting an in-depth confidential interview to explore the teen’s environment and any risky or dangerous behavior or thoughts. The aim of this project is to analyze the first year of teen clinic so as to show others who may be interested in starting a clinic of this kind what exactly it may entail. Specifically, the research objectives were to create a raw database of information from the first year of UNTHSC's Teen Clinic (stripped of identifiers); discover the population served; and analyze the depression and risky sexual behavior populations and the interventions used for them.

Methods: Retrospective data collection and analysis. Created a raw database of all cases seen in teen clinic from 06/04/15 to 06/24/16. Collected and placed the following coded information into a protected Excel file: Age, Sex/gender, Referral Source, Chief Complaint (CC), History of Present Illness (HPI), Assessment, Medical Intervention, Psychiatric Intervention, Outcomes, Provider, and any Miscellaneous Information. Total of 196 encounters and 116 patients were included in the present study with no exclusion criteria. Analyzed chief complaint (CC), history of present illness (HPI), and assessment. Separately analyzed CC, HPI, assessments, and interventions of the Depression/Adjustment Disorder and Hypersexual Behavior populations.

Preliminary Results: The top four CC, HPI, and assessments seen were determined. CC: Well child check (80), follow up (44), establish teen clinic (27), and depression (17); HPI: depressive symptoms (56), family instability (45), acute symptoms (31), well child check (29); Assessment: well child check within normal limits (72), depression (49), asthma/allergies (22), obesity (21). Populations with depression/adjustment disorder and hypersexual behavior were analyzed. In the small hypersexual group, there was successful intervention in 44% of females seen (i.e. Nexplanon placement). We found that in the depressive group 54.8% followed up.

Conclusions: In its first year alone, Teen Clinic addressed a variety of unique issues not often explored in a typical pediatrician’s visit- most importantly (indicated by the frequency seen) symptoms of depression and adjustment disorder. Additionally, many teens were recommended for follow up, and many actually came back, successfully establishing a medical home.

There are many possibilities for future studies, including, but not limited to: correlational analysis between family issues and risk taking behavior; analysis of patient compliance (by tracking follow up visits); analysis of outcomes from various interventions; and continuing the analysis of interventions in the hypersexual and depressed groups.

Sponsor: N/A
IRB/IACUC#: 2018-021
Program Review for UNTHSC Clinical Trials - Guidelines for Human Gene Transfer Trials Research Involving Recombinant and Synthetic DNA

Purpose:

Human Gene Transfer (HGT) clinical trials are a rapidly progressing field that involves the introduction of a genetic sequence into a human subject for research or diagnostic purposes. Clinical HGT are regulated by the U.S. Food and Drug Administration (FDA) at the federal level and to oversight by institutional review boards (IRBs) and institutional biosafety committees (IBCs) at the local level before human subjects can be enrolled. In addition, at present, all researchers and institutions funded by the National Institutes of Health (NIH) are required by NIH guidelines to submit human gene transfer protocols for advisory review by the NIH Recombinant DNA Advisory Committee (RAC). NIH guidelines are the definitive reference for Recombinant and Synthetic DNA research in the United States and should have adopted by UNTHSC. The purpose of this research is to review the clinical trials program at UNTHSC and incorporate recent revised NIH guidelines on clinical trials involving Recombinant and Synthetic DNA.

Methods:

NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules, UNTHSC IBCs Biosafety Manual, UNTHSC IRBs Guidance for Human Subject Investigators, have been used as core materials to review.

Results:

UNTHSC IBC webpage was updated with additional information from the review. Existing clinical trial protocols will be reviewed and validated with the department of clinical trials to confirm that at current active clinical trials at UNTHSC does not involve any HGT trials.

Conclusions:

For future clinical trials, the material developed based on the review will be shared with investigators, clinical trials department, IRB and IBC webpage.

Sponsor: N/A

IRB/IACUC#: N/A
Major Mental Illness: Resources in Tarrant County

Purpose: Our project sought to present patient resources in Fort Worth and Tarrant County that focus on major mental illness, which affects 1 in 5 adults yearly in the United States. This includes, but is not limited to: major depressive disorder, bipolar disorder, post-traumatic stress disorder, schizophrenia, eating disorders, and substance abuse disorders. There is a higher prevalence of major mental illness among homeless, prisoner, and veteran populations, and in Tarrant County high poverty and uninsured rates contribute to prevalence rates higher than the national averages. Additionally, there are shortages of mental health care providers in Tarrant County and Texas overall.

Methods & Results: A thorough investigation and review of resources in Tarrant County was conducted. Among the resources found in Tarrant County, several are branches of larger state or national organizations that provide extensive support and advocacy for, and education about mental illness. In addition to providing information on Tarrant County resources, we included information on resources for medical and health professions students on the UNT Health Science Center campus who may be living with one of these illnesses. High prevalence of physician burnout and maximal stress contributes to mental instability and increased mental illness prevalence among physicians and providers.

Conclusions: Based on what we found in our search for resources, we concluded that there needs to be an increase in the number of mental health providers, an increased focus on advocacy and awareness about mental illness and health care, and an open dialogue about the real consequences of untreated mental illness in all populations.
Factors Influencing Patient Willingness to Participate in an Outpatient Pharmacy Transition of Care Program

Purpose: The purpose of this study is to identify any inpatient hospital controllable factors that influence a patient’s willingness to participate in an outpatient transition of care program.

Methods: A qualitative debrief analysis was conducted to identify strengths and weaknesses of recruitment efforts after the conclusion of a study into a transition of care program. All recruitment personnel involved this study conducted at Medical City Fort Worth were asked to complete a survey battery. It consisted of ten questions designed to elucidate a full picture of the challenges and successes the recruiters encountered during patient interaction experiences. Researchers then read the responses three times. During the first reading the researchers took no notes. On the second reading researchers marked instances of prevailing ideas. On the third reading researchers transferred the most prevalent ideas to separate notes. Researchers then compared all noted ideas identified by the group. From those ideas, three themes pertinent to the profession of pharmacy emerged.

Results: The first theme was timeliness. Recruiters unanimously reported requiring multiple visits to obtain patient consent for study participation. Multiple recruiters reported that newly admitted patients were more likely to be overwhelmed by their circumstances while patients who had been scheduled for discharge were willing to discuss medication related programs and services.

The second theme was concern about changing pharmacies. More than eighty percent of recruiters reported encountering patient objections related to changing their existing pharmacy provider. One prevailing idea included in this theme is that the community pharmacist is seen as a trusted health-care provider. Recruiters reported that once patients understood that a program pharmacist was going to take personal responsibility for managing their medications that they became more willing to participate.

The third theme was ensuring caregiver or family involvement in the decision-making process. Recruiters unanimously reported the need for the patient's social support network to be included in the discussion and decision regarding outpatient health-care.

Conclusions: When designing voluntary outpatient medication management programs three themes should be considered to ensure patient involvement: 1. Reduce redundant and non-productive patient encounters by discussing programs closer to discharge or as part of the discharge medication counseling, 2. Be prepared to address concerns over changing, and pharmacies by describing the personal role the pharmacist will be playing in the patient's care. 3. Lastly, ensure that the patient's primary caregiver or social support person in present to discuss changes to outpatient medical care.
**Sponsor:** Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R25HL125447 (to Dr. J.K.Vishwanatha). The content is solely the responsibility of the authors

**IRB/IACUC#:** 2016-112
PATIENT SAFETY CULTURE IN SKILLED NURSING FACILITIES

PURPOSE

Skilled nursing facilities (SNF) have an increasingly frailer and more dependent patient population with a high risk of re-hospitalization from preventable adverse events. Developing a culture of safety is a core component to clinician and staff behaviors that affect safety, quality, and patient outcomes, although little is known about improving patient safety in long term care settings. With a goal of improving the safety culture and quality of care provided in SNF settings, UNTHSC Center for Geriatrics developed and implemented the evidence-based interprofessional Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS) to address falls risk reduction at skilled nursing facilities in Fort Worth, Texas.

METHODS

We administered the Agency for Healthcare Research and Quality (AHRQ) Nursing Home Survey on Patient Safety Culture Brookdale Broadway Plaza (n=36), the Stayton (n=26) between August and October 2017. Survey results across twelve composites of patient safety culture were used to inform the development and delivery of a TeamSTEPPS Long Term Care 2.0 training series focused on falls risk reduction. The first training session delivered in October 2017 for direct care staff (n=47) provided an overview of the TeamSTEPPS model and communication tools, and an introduction to falls risk reduction in long term care settings. A second session for direct care staff (n=37) delivered in December and January provided additional training in TeamSTEPPS strategies and development of a communication tool to aid in fall risk reduction. Initial evaluation of knowledge and skills of trainees included a Likert scale survey.

RESULTS

Survey analysis identified that most staff believed their residents were safe in their facility (89% Brookdale, 91% Stayton, 82% Trinity) and they would recommend their facility to others (76% Brookdale; 80% Stayton). The lack of communication regarding residents (Brookdale 60%; Stayton 48%) was prevalent in both facilities and most direct care staff felt they were not considered members of the care team (61% Brookdale; 50% Stayton). Initial evaluation of TeamSTEPPS training showed that a majority (92-100%) were highly confident they could describe objectives related to the TeamSTEPPS program and falls awareness and prevention. As a result of the training, an action plan and communication tool was developed with input from the trainees to ensure continuity of care, improve communication, and decrease falls. Using a Plan-Do-Study-Act continuous improvement cycle, this checklist will be implemented by designated facility personnel. A post evaluation using the patient safety culture survey will be administered.

CONCLUSIONS
The implementation of TeamSTEPPS at SNF facilities demonstrated benefits to staff in improving their quality of care and ability to work collaboratively for the good of the patients. We anticipate that SNF will utilize TeamSTEPPS principles to develop, implement and sustain effective patient safety interventions.

**Sponsor:** N/A  
**IRB/IACUC#:** 2018-016
SMITH-LEMLI-OPITZ SYNDROME & IMPAIRED CHOLESTEROL METABOLISM

INTRODUCTION

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive disorder due to mutations in the \textit{DHCR7} gene, impairing 7-dehydrocholesterol reductase (DHCR7) and cholesterol synthesis. Patients typically present with low cholesterol and high 7DHC (7-dehydrocholesterol, a toxic precursor) levels, although these values may be normal. SLOS is characterized by distinctive facial and autistic features. Severity depends on baseline cholesterol levels from fractional synthesis by DHCR7 with wildtype-like activity. We present a case and current management recommendations.

CASE PRESENTATION

A 15-yr-old male with SLOS was referred for short stature and delayed puberty. He has a history of a cleft palate repair, hemangioma removal, gastrostomy button placement, hypospadias, and umbilical hernia repairs. A younger brother, suspected to have SLOS, died young. Physical exam revealed a height and weight <1\textsuperscript{st} percentile, coarse facial hair, dental dysplasia and malalignment, widely spaced nipples, a broad chest, an undescended left testicle, and global delays. Laboratory results included normal LDL-C (low-density lipoprotein cholesterol) levels of 84 mg/dL (ref. range/dL), atypical of SLOS. He is thought to have residual wildtype-like DHCR7 activity.

RESULTS

Cholesterol supplements may improve clinical symptoms with minimal side effects. However, studies with standardized methods analyzing cognitive impairment have shown no improvements. Because cholesterol does not cross the blood-brain-barrier (BBB), CSF cholesterol and 7DHC are not altered after supplements. Studies of simvastatin (crosses the BBB), however, have shown improved CSF cholesterol and 7DHC levels, and developmental and behavioral symptoms in mild SLOS (recognized by the Aberrant Behavior Checklist-Community irritability score). Although simvastatin inhibits HMG-CoA reductase, it is hypothesized that the paradoxical elevation in CSF cholesterol is due to increased expression of mutant \textit{DHC7R} with wildtype-like activity, from increased synthesis of the regulatory protein SREBP2 by simvastatin.

CONCLUSION

SLOS is an autosomal recessive disorder that impairs DHCR7 function. Severity is dependent on cholesterol and 7DHC levels. Management with cholesterol supplementation may not alleviate SLOS-related developmental deficits. Simvastatin, however, may be helpful and should be considered for patients with mild presentations of SLOS that have residual wildtype-like activity of DHCR7.

\textbf{Sponsor:} N/A
\textbf{IRB/IACUC#:} CCHCS-IRB
The Development of a Framework on Approaches to Adherence Best Practices for Health Plans: A Systematic Review

Background:

Roughly 50% of all patients do not adhere to their medication regimens. Root causes for nonadherence are complex and usually involve a variety of factors. A one size fits all approach to intervention programs would likely only yield suboptimal outcomes. Tailoring interventions according to patient characteristics can increase the likelihood of adherence intervention effectiveness.

Purpose:

The objective of this study was to review the literature within the past decade to develop a framework for best practices in health plan use of medication adherence interventions, with respect to patient perceptions, cultural competence, patient characteristics, and timing and frequency.

Methods:

This systematic review was conducted using PubMed, SCOPUS, Cinahl Complete, and Global Health databases to obtain articles published in the US from 2007 to 2017. Search terms used included: “medication adherence”, “interventions”, “program evaluation”, “text”, “phone”, “mail”, “visits”, “in person”, “acceptability”, “patient preference”, “cultural competency”, “health literacy”, “patient perceptions”, “smartphone”, “electronic mail”, “support groups”, “drug”, “medication” and “efficacy”. Abstracts were screened according to broad inclusion and exclusion criteria. Articles were read in detail and graded by Oxford Evidence-Based Grading System. Selected articles were categorized by adherence intervention: telephone outreach, provider-centric, and face-to-face visits.

Results:

Preliminary findings based on 79 articles retrieved thus far show that studies assessing patient perceptions of telephone interventions in the form of text messaging and mobile apps, prove high acceptability. Face-to-face visits in the form of behavioral-based family counseling have high acceptability among adolescent populations while provider-centric interventions appear to be highly dependent on the patient-provider relationship. Studies assessing cultural competence primarily show usefulness in provider-centric interventions and face-to-face visits as compared to telephone, and trend toward better efficacy in immigrant and low health literacy populations.

Conclusion:

Next steps in the conduct of this research will include an examination of the impact of patient characteristics (race, age, gender, marital status, SES and disease severity) on the effectiveness of adherence interventions.

Sponsor: N/A
IRB/IACUC#: N/A
Bleeding diathesis in a patient with a novel mutation in SERPINF2: A case study of alpha-2 antiplasmin deficiency

Background: Alpha-2 antiplasmin is a serine protease inhibitor that inactivates plasmin and prevents premature breakdown of fibrin clots. Deficiency of this enzyme can lead to spontaneous bleeding and hemophilia-like symptoms, despite normal coagulation and platelet function studies. We present a case of congenital alpha-2 antiplasmin deficiency to emphasize the importance of recognizing a patient with bleeding symptoms despite normal coagulation assays and to report a novel SERPINF2 gene mutation as a cause of this disorder.

Case Information: A 7-month-old patient presented with a hemarthrosis of the right knee that was assumed to be septic arthritis, despite negative cultures of the bloody synovial fluid. She experienced significant bruising and spontaneous hematomas, necessitating a hematologic consultation. Complete blood count (CBC), Von Willebrand Factor (VWF) activity and antigen, prothrombin time (PT), partial thromboplastin time (PTT), thrombin time, platelet function analysis, and fibrinogen levels were all normal. At 3 years of age, she had a second suspected hemarthrosis of the right knee, prompting the following tests: plasminogen activator inhibitor-1 levels, euglobulin lysis time, factor XIII activity and platelet aggregation studies. All tests showed normal results. In addition, she had two episodes of hemorrhage after a tooth extraction, both instances required red blood cell and fresh frozen plasma transfusions. Whole exome sequencing revealed a novel homozygous mutation in the SERPINF2 gene. Alpha-2 antiplasmin activity was then measured at A), has not been previously reported in patients with alpha-2 antiplasmin deficiency. Family history was positive for consanguinity. These findings suggest that this mutation has likely been present in several generations of this patient’s family and follows the pattern of an autosomal recessive disorder.

Conclusions: This case highlights the difficulties in diagnosing bleeding disorders that involve the fibrinolytic pathway. The previously unreported pathogenic mutation of the SERPINF2 gene may provide valuable insight into the molecular mechanisms of alpha-2 antiplasmin deficiency.
An 11-Year-Old Female with Short Stature, Developmental Delay, and Bilateral Cataracts

Pseudohypoparathyroidism (PHP) is a rare, autosomal dominant disorder characterized by an end-organ insensitivity to parathyroid hormone (PTH). 1,2,3 Children with PHP typically present with symptoms of hypocalcemia, such as tetany and seizures.

The most common form of PHP is 1A, caused by a loss of function mutation in the GNAS gene, which primarily affects PTH and possibly other hormones that share the same signal transduction. 3,4

In addition to symptoms of hypocalcemia and hormonal resistance, patients with PHP1A present with one or more features of Albright hereditary osteodystrophy (AHO), including short stature, subcutaneous ossifications, obesity, rounded face, mental deficit, and brachydactyly of either the 4th or 5th phalanges of the hands, feet, or both.

We report a child who presented with features of PHP1A, discuss the diagnosis, and current recommendation of this rare condition.

Sponsor: University of North Texas Health Science Center and Cook Children’s Pediatric Research Program (PRP)

IRB/IACUC#: CCHCS-IRB
Age and sex differences in childhood and adulthood obesity association with phthalates: Analyses of NHANES 2011–2014

Purpose: To examine the relationship between urinary phthalates and obesity in children/adolescents and in adults using data from NHANES 2011-2014.

Methods: Using the National Health and Nutrition Examination Surveys (NHANES) 2011-2014, data files on ten urinary phthalates and obesity in children/adolescents (aged 6-19 years old) and in adults (20 years and older) were retrieved. Urinary phthalates were grouped as low molecular weight (LMW) phthalates, High Molecular Weight (HMW) phthalates, Di-2-ethylhexyl phthalates (DEHP) and categorized using weighted quartiles. Children/adolescents were classified as underweight/normal, overweight and obese using the BMI z-score. Adults were classified similarly using BMI measures of 29.9, respectively. A multinomial logistic regression was conducted to determine the association of urinary phthalates and obesity while controlling for covariates. Participants with missing covariates, pregnant women and breastfeeding women were excluded.

Results: Using multinomial logistic regression, the 3rd quartile for LMW and the 4th quartile for DEHP had statistically significant associations with being overweight in children/adolescents. The 3rd quartile for LMW was associated with being overweight in female children/adolescents and the 4th quartile for DEHP was associated with being overweight in male children/adolescents. The 4th quartile of individual phthalate MECPP was found to result in increased odds of being overweight in the female group and in children overall. The highest quartile for MEHHP was also significantly associated with obesity for children overall and for males. There were no statistically significant associations between urinary LMW, HMW and DEHP concentrations and obesity in adults, even when stratified by gender. Analyses of the individual phthalate components of LMW indicated an association between the 4th quartile of MnBP and overweight among female adults. No association was found in other individual phthalates and prevalence of obesity in adults.

Conclusion: Urinary concentrations of LMW and DEHP are associated with increased rates of overweight in children/adolescents and there is a sex difference in this association. There is no apparent association between urinary phthalates and obesity in adults.

Sponsor: N/A
IRB/IACUC#: 2017-104
Treating Mood Symptoms: Is the Therapeutic Response in Veterans At-Risk for mTBI Similar to Veterans with No-Risk for mTBI?

Purpose: Active theater combat veterans serving in Iraq and Afghanistan wars encounter more blasts and explosions than any previous war which increases their risk for mild traumatic brain injury (mTBI). Returning veterans often seek behavioral health services to help them overcome traumatic wartime experiences associated with depression and anxiety. Cognitive behavioral therapy (CBT) is a ‘gold standard’ treatment strategy for returning veterans. However, there are few studies comparing the response-to-treatment of CBT for depression and anxiety between veterans at-risk for mTBI versus those with no-risk. We hypothesize that active theater veterans at-risk for mTBI will have a more severe posttraumatic stress disorder (PTSD), more depression and anxiety and will have a slower response-to-treatment time than veterans with no-risk.

Methods: In this hypothesis-generating pilot study, we examined the clinical characteristics of veterans at-risk for mTBI compared to veterans with no-risk and evaluated the longitudinal effectiveness of 12-weeks of CBT and the response-to-treatment using secondary data analyses. Data from male veterans (24-57-years old) serving in Iraq and Afghanistan of all race/ethnicities receiving CBT were analyzed as no women in this sample served in active theatre. The PTSD checklist, Beck Depression Inventory, and Beck Anxiety Inventory were used to examine response-to-treatment. Chi-square, ANOVA, and repeated measures ANOVA were used to evaluate between-group differences.

Results: Veterans at-risk for mTBI (n=136) had more severe PTSD, higher depression and anxiety scores than no-risk veterans (n=38). Almost 61% of veterans at-risk for mTBI had PTSD compared to 26% of veterans at no-risk. All veterans experienced reduced depression and anxiety symptoms with 12-weeks of therapy [Wilk’s Lambda=.59, F(4,76)=13.27, p=0.0005, n²=.41]. However, mood scores for veterans at-risk for mTBI were almost 50% higher at baseline, 6- and 12-week time points than veterans at no-risk.

Conclusions: These results inform clinical practice about the psychological consequences of serving in active theater and the long-term treatment needs of veterans with mTBI and PTSD. Clinicians who treat returning veterans should inquire about active theater exposures to blasts and explosions which predisposes them to risks for mTBI and severe PTSD. Clinicians should expect longer and slower responses to CBT in active theater veterans compared to non-combat.

Sponsor: Recovery Resource Council
IRB/IACUC#: 2014-058
Kinematic Analysis of Sagittal Plane Stability of Delta Frame External Fixation

Purpose: External fixation with a delta frame construct is the most common construct used for temporizing patient distal tibia and ankle injuries. While these constructs may be the most common there are numerous variations that are often performed based on surgeon preference. The inclusion or exclusion of a Posterior slab or 1st metatarsal pin to the construct is variable amongst surgeons and have little data to support their use aside from anecdotal evidence.

Methods: 10 Fresh Frozen Cadavers were secured to a custom-made rig that held the tibia rigid and allowed the application of a standard delta frame external fixator. The specimens had a 2 cm segment of bone resected near the ankle plafond to simulate a highly unstable distal tibia or pilon fracture. The ankle was then loaded with a 10 lb weight from the great toe and 3D kinematics were recorded using an electromagnetic tracking system with 6 degrees of freedom. The 4 construct comparisons were: 1. Delta frame 2. Delta frame with 1st metatarsal pin 3. Delta frame with Posterior slab 4. Delta frame with 1st metatarsal pin and Posterior slab

Results: The delta frame construct without any additions was less stable than all other constructs with statistical significance in the sagittal plane with regards to flexion/extension rotation. The most stable construct was a delta frame with 1st metatarsal pin and Posterior slab. The most cost-effective measure to add sagittal plane stability was the addition of the Posterior slab splint.

Conclusion: Delta frame stability in the sagittal plane can be cost effectively augmented by the addition of a Posterior slab. The addition of both a Posterior slab or 1st metatarsal pin were able to significantly add stability to the base construct and the combination of the 2 were able to achieve highest stability.

Sponsor: N/A
IRB/IACUC#: N/A
Pharmaceutical Sciences (Abstracts in the 1900s)

1900 - Poster

**Classification:** Postdoctoral Fellow

**Presenter:** Hamed S Hayatshahi

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Probing protein allostery through residue perturbation maps

Protein allostery has been well accepted to be an intrinsic feature of all dynamic proteins. A perturbation at one site of the protein could distantly affect another site. The residues involved in these sites are considered as allosteric residues. Here, we argue that all residues in a protein are allosteric residues. We used hybrid models including molecular dynamics simulations and machine learning components to investigate whether a single or multiple properties of protein residues are changed upon ligand binding in PDZ3 domain. Also, we tried to understand whether various residues are affected similarly or in different ways when the ligand is bound. Our deep neural networks and random forests trained with different residue properties of molecular dynamics trajectories revealed that not only many properties of residues are affected upon ligand binding, but also each residue is affected through perturbation of its various properties, which makes the residue distinguishable from other residues. In other words, upon perturbation, different properties of each residue are affected at distinct extents, demonstrating that all residues are allosteric residues. According to our findings in this model protein, we defined a “residue perturbation map” as a two-dimensional map that fingerprints a protein based on the extent of perturbation in different properties of all its residues in a quantitative fashion. This “residue perturbation map” provides a novel way to systematically describe the protein allosteric effects of each residue upon perturbation.

**Sponsor:** N/A

**IRB/IACUC#:** N/A
Update of Population Pharmacokinetic Model for Tenofovir (TFV) in HIV-1-Uninfected Members of Serodiscordant Couples

Purpose: Oral tenofovir disoproxil fumarate (TDF) has demonstrated success in HIV pre-exposure prophylaxis (PrEP) among high risk groups. A population pharmacokinetic model (PoP PK) was reported by us using the Partners PrEP trial data in serodiscordant couples. The objective of current work was to update, the prior population pharmacokinetic model of tenofovir with pharmacokinetic and adherence data from the Demonstration project.

Methods: Two plasma samples were collected from study subjects and their dosing data was extracted from medication event monitoring system (MEMS®) records. Data from the Demonstration project and the Partners PrEP trial were combined in the analysis. The PoP PK model developed was a two compartment model parameterized with first order absorption rate constant (Ka) and absorption lag-time (Alag), clearance (CL), central and peripheral volumes (Vc & Vp) and inter-compartmental clearance (Q). Creatinine clearance was included as covariate on CL. Exponential error was used for between-subject-variability (BSV) on parameters. Residual error was modeled as combined additive and proportional error model. Gibiansky’s correction for bio-availability was included in the model to adjust for dosing errors. Model was qualified with visual predictive check (VPC, n=1000 samples) and bootstrap procedure (n=500 iterations). NONMEM software (version 7.3) was used for modeling and R software package (version 3.4.2) was used for data management and plots.

Results: A total of 1,592 TFV levels from 565 subjects were used for model development. The final fixed effect parameter estimates were: CL-47.8 L/h; Vc – 214 L; Vp – 512 L; Ka – 1.7; Q – 300 L/h and lag time was 0.69 hr. Relative standard Error (RSE) of estimates were in the range of 2 to 32% for all parameters. Final random effects parameters were BSV on clearance (23%), on Vc (76%), on Ka (79%) and on additive error (150%). RSE of random effect parameters ranged from 12 to 22%. Additive error (SD) was 19 ng/mL and proportional variability was 21% (CV). Goodness of fit plots showed that the model did not have major bias. VPC showed that the distribution of model simulated data agreed with observed data.

Conclusion: Tenofovir PoP PK model was updated with the new data from demonstration project. The model will be utilized for interpreting concentration based threshold of protection using MEMS® adherence patterns and text messaging on sexual activity information available in the trial.

Sponsor: National Institute of Health
IRB/IACUC#: 2016-133
Development and characterization of in situ self-assembly nanoparticles for Oral Docetaxel

Purpose: Docetaxel (DTX) is a chemotherapy drug that can be used for different type of cancers. Due to polysorbate 80, the excipient in the formulation, acute hypertensivity reaction is observed after intravenous administration. The development of oral formulation for DTX has always been problematic as the bioavailability of the drug is shown to be low due to P-glycoprotein efflux transporters and the intestinal metabolism by CYP3A4 enzymes. The objective of this study is to develop novel DTX in situ self-assembly (ISNP) granules to enhance bioavailability of DTX for oral administration.

Method: The novel nanoformulation of DTX was developed by nanotechnology utilizing the proportional ratio of the components of D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS), Miglyol 812, Aeropearl 300 and DTX. The particle size, drug loading and drug entrapment efficiency of the nanoparticles (NPs) were characterized using high-performance liquid chromatography and Delsa Nano C Particle Size Analyzer.

Results: The proportional ratio among the components, which optimized the drug loading and drug entrapment efficiency, was successfully identified. The drug loading and entrapment efficiency of DTX delivered in ISNP were 10% and 85% respectively. The particle size of DTX ISNPs was achieved to be around 150 nm with the polydispersity index less than 0.3.

Conclusion: DTX ISNPs were successfully developed with the composition that delivers the optimal drug loading and drug entrapment efficiency. Novel DTX ISNPs could enhance the absorption and bioavailability of the drug for oral administration as well as reduces the risk of acute hypersensitivity reactions, which improves patient adherence and reduces hospitalization.

Sponsor: N/A
IRB/IACUC#: N/A
The Stability of Quetiapine Fumarate 10 mg/mL Compounded Oral Suspension in Ora-Blend and Ora-Sweet Vehicles Over Time at Two Temperatures

Purpose: Quetiapine fumarate (QF) is an atypical antipsychotic agent that is used off-label for the treatment of delirium in critically-ill children. QF is commercially available as immediate and extended-release tablets for oral administration. Although there is a published 40 mg/ml compounded suspension, this is not suitable for small doses, and there is no stability data available for QF compounded suspension. Therefore, the objective of this study was to evaluate the stability of 10 mg/mL QF compounded oral suspension in Ora-Blend (OB) vehicle and Ora-Sweet (OS) vehicle by analyzing drug contents, dissolved drug in selected vehicles, pH, visual appearance and odor at two temperatures up to 90 days.

Methods: QF compounded suspensions (10 mg/mL) were prepared from QF commercial tablets in either OB or OS vehicle and were stored in plastic amber bottles at either 22°C or 2°C. At day 0, 7, 60 and 90, three bottles from each condition were used to prepare samples for the high-performance liquid chromatography (HPLC) analysis that was developed and validated. The drug contents were measured by directly mixing QF suspension with MeOH:H2O (v/v) and diluting the supernatant with MeOH after centrifugation to a detectable concentration for HPLC analysis. To measure dissolved QF, QF suspension was centrifuged and then QF in the supernatant was measured by HPLC. pH was measured by a pH meter, and physical characteristics were analyzed based on the changes in color and odor.

Results: The QF drug contents in OB and OS for 90 days were not significantly different compared to day 0 at two temperatures. QF in OB remained dissolved over time at two temperatures, whereas QF in OS was precipitated out at day 7 and 90. The pH of both OB and OS preparations was consistent from day 0 to day 90. There were no significant differences in visual appearance or odor for both OB and OS preparations overtime at two temperatures.

Conclusions: Based on the results of drug contents, dissolved drug, pH and physical characteristics, QF compounded suspensions in OB were stable at two temperatures for up to 90 days. Compared to OS, OB is the better vehicle to prepare QF compounded suspensions.

Sponsor: N/A
IRB/IACUC#: N/A
Evaluation of the Sensitivity of Concluding Bioequivalence Using Stochastic Simulation and Estimation

Purpose: Single dose (SD) bioequivalence (BE) studies can fail statistical criteria by maximum concentration (Cmax). Population pharmacokinetic (PoP PK) model based simulations are used in such instances to predict steady-state (SS) concentrations to evaluate BE criteria on simulated data. We evaluated the sensitivity of such PoP PK model based method to find true formulation differences in a simulation study.

Methods: Stochastic simulation and estimation (SSE) method was applied. The structural model was a one compartment model with 1st order absorption. An exponential error (15% CV) for between subject variability and proportional error (15% CV) model for residual variability was assumed. PK studies (n=200) having 1000 virtual subjects dosed with test and reference formulations were simulated with NONMEM® software (v. 7.3.0) for SD and SS. The rate of absorption (Ka, hr⁻¹) parameter varied between test and reference formulations to simulate passing and failing PK profiles for BE criteria. Different Ka combinations for test and reference formulations include 0.1/1, 0.2/1, and 0.5/1.5. Simulated PK profiles were analyzed using PKNCA (v. 0.8.4) package in R (v 1.0.143) software to conduct a non-compartmental analysis and iterated 200 times. The resulting Cmax and AUC were assessed using the Welch 2-sample t-test function to conclude BE. A 90% confidence interval of AUC and Cmax falling between 0.8-1.25 was set a priori as BE criteria. Lastly, the sensitivity of the PoP PK model based simulation method for concluding SD and SS based BE conclusion was calculated from 200 independent simulated studies.

Results: Bioequivalent formulations of SS and SD that were designed by same absorption rate parameter met BE criteria set a priori for Cmax and AUC. Varying Ka parameters between test and reference formulations, with Ka combinations of 0.1/1 and 0.2/1, only failed BE criteria for Cmax on SD. The Ka parameter combination 0.5/1.5 did not result in failed Cmax on SD and is not considered as true failed criteria by design. Of the 200 simulated datasets in the fail BE criteria by design on SD, all of them passed the a priori BE criteria for Cmax for SS simulations.

Conclusion: The PoP PK model based simulation method may not be sensitive to study BE of Cmax at SS after initial failure of two SD drug formulations. True differences in the formulation Ka cannot be detected in SS simulations. The method is still applicable for concluding the clinical relevance SS Cmax.

Sponsor: N/A
IRB/IACUC#: N/A
Evidence for improved motor function by ceftriaxone despite striatal tyrosine hydroxylase loss following nigrostriatal lesion

Purpose: The beta-lactam antibiotic, ceftriaxone, attenuates tyrosine hydroxylase (TH) loss in striatum in rodent Parkinson’s disease (PD) models when given early after nigrostriatal lesion. This protection may be related to the well-known properties of ceftriaxone to increase expression of the glutamate transporter, GLT-1, which increases glutamate uptake. Ser19 TH phosphorylation, which is modulated by glutamate and Ca²⁺-influx, increases in proportion to TH loss following nigrostriatal lesion and may predispose TH to premature degradation via the ubiquitin-proteasome pathway. Here we evaluated if ceftriaxone could partially restore striatal TH loss, concomitant with a decrease in motor impairment, when administered 1 week after lesion induction.

Methods: The ability of ceftriaxone to decrease motor impairment was evaluated after evidence of motor impairment by evaluation of forepaw adjustment steps (FAS) and open-field locomotor activity. Ceftriaxone (200 mg/kg, i.p.) was given intermittently on days 7-13, 21-27, and 35-38 post-lesion. Motor function 7 days after lesion induction was used as a baseline to evaluate if ceftriaxone could reduce motor impairment out to 40 days post-lesion.

Results: There was a significant increase in FAS taken, with an overall 45% increase in mean FAS post-lesion compared to the day 7 baseline. Locomotor activity (ambulatory count and total distance) increased at the end of the study (38 days post-lesion) against the day 7 baseline following ceftriaxone. >90% striatal TH protein loss was evident regardless of whether the rats received ceftriaxone or saline injection. However, in the substantia nigra, there was a significant increase in TH expression in the side contralateral to lesion in the ceftriaxone group.

Conclusion: Taken together, these results suggest that ceftriaxone-mediated protection against locomotor decline, after the establishment of a nigrostriatal lesion, may be independent of any preservation or possible restoration of striatal TH.

Sponsor: N/A
IRB/IACUC#: 2014/15-26
Combination Therapy with Short-Contact Topical Calcipotriene and 5-FU For Actinic Keratosis

Background: Actinic keratoses (AKs) are precursor lesions to squamous cell carcinoma that arise from dysplasia of keratinocytes, which is enhanced by long-term ultraviolet radiation exposure. Treatment of actinic keratoses has traditionally involved cryotherapy, or various topical therapies such as topical 5-fluorouracil (5-FU) monotherapy, or combination therapy with cryotherapy. Because of irritation with use of topical 5-FU, short-contact therapy with 5-FU in combination with cryotherapy has been reported. Vitamin D derivatives have also been reported as systemic anti-cancer agents, though clinical data for usage is limited mainly due to hypercalcemia as an adverse effect and dose-limiting factor. Recent research has suggested that topical Vitamin D derivatives such as calcipotriene may be safe and efficacious agents for the treatment of AKs.

Objective: The aim of this study was to evaluate efficacy and safety of short-contact topical treatment with calcipotriene and 5-FU with cryotherapy in the treatment of AKs. Combination short-contact calcipotriene and 5-FU with cryotherapy will be compared to short-contact 5-FU with cryotherapy and cryotherapy alone to determine differences in efficacy and safety between the treatment modalities.

Methods: Subjects were identified as eligible for inclusion in this study based on a clinical diagnosis of actinic keratosis and treatment with cryotherapy, 5-FU, and/or topical calcipotriene between 2016 to 2018. The patients were divided into three treatment groups: 1) short-contact combination treatment with calcipotriene and 5-FU with cryotherapy, 2) short-contact 5-FU and cryotherapy, and 3) cryotherapy alone. Patients were assessed for baseline lesions in the face, scalp, upper extremities, chest, back, and lower extremities, and again at 1 month follow-up, 3 months follow-up, and 6 months follow-up. An analysis of covariance (ANCOVA) model with terms for treatment and baseline lesion count as covariate was used to compare post-treatment lesion count between treatment groups estimated at 95% confidence intervals (95% CI).

Results: Data was collected on 50 patients in each subset. After adjusting for imbalances in baseline count, a statistically significant reduction in number of AK lesions occurred after 6 months of treatment with short-contact combination treatment with calcipotriene and 5-FU with cryotherapy in comparison to short-contact 5-FU with cryotherapy and to cryotherapy. The mean total lesion count at month 6 in the short-contact combination treatment with calcipotriene and 5-FU with cryotherapy was significantly lower than in the other 2 subsets.

Conclusions: Addition of topical calcipotriene to short-contact combination treatment of topical 5-FU with cryotherapy may result in improved long-term outcomes for patients with actinic keratoses. Larger series must be done to confirm increased efficacy and safety.

Sponsor: Arling

IRB/IACUC#: SCHULMAN IRB-SAIRB-17-0077
Population Pharmacokinetics of Pemetrexed in Adult Non-Small Cell Lung Cancer Patients in India

Purpose: Pemetrexed (PEM) is indicated for the treatment of non-small cell lung cancer (NSCLC) in combination with cisplatin. The study aimed to characterize pharmacokinetics (PK) and effects of covariates on PK of PEM using a population pharmacokinetic (PPK) approach.

Methods: PPK analysis was performed using plasma samples from 85 patients following 500 mg/m² IV infusion. The model was developed using NONMEM® (v.7.3.0). Diagnostic plots were generated with packages XPOSE and ggplot2 in R (v.3.4.2). The structural model was a two compartment model parameterized with clearance (CL), central and peripheral volume of distribution (V1 & V2), and inter-compartmental clearance (Q). Exponential error model was assumed for inter-individual variability (IIV) in PK parameters. Residual variability (RV) was modeled as combined additive (ADD) and proportional (PROP) error model. The estimation method was the stochastic approximation expectation maximization (SAEM). Standard errors (SE) and objective function value were calculated using Monte Carlo importance sampling method. Full covariate model approach was utilized by specifying clinically meaningful covariates in the model. Power model was used to describe covariate relationships. Markov chain monte carlo Bayesian analysis (BAYES) was used to compute 95% credible intervals (CI) for the Posterior distribution for covariate effects. This CI was used to reduce the full covariate model by eliminating the covariates whose CI included null hypothesis.

Results: Total of 850 PEM levels were used for model development. The final model included weight allometrically scaled to V1, V2 and Q. The fixed effect parameter estimates were CL-3.13 L/h; V1–5.54 L; V2–7.01 L and Q–5.42 L/h. Covariates that retained significance following BAYES CI’s: CrCl on CL, Sex on CL and Albumin on V1 with estimates of 0.52, 1.22 and -1.46 respectively. IIV on CL, V1, V2 and Q were 52%, 51%, 122% and 88% respectively. Relative SE of estimates were in the range of 10 to 43 % and 18 to 128% for fixed and random effect parameters respectively. ADD (SD) was 0.54 µg/mL and PROP RV was 29%. Goodness-of-fit plots showed no major bias in the model. VPC showed agreement between distribution of model simulated and observed data.

Conclusion: PPK model for PEM in Indian subjects was successfully developed using full covariate modeling approach. The covariate relationships identified could be used to individualize dosing based on patient characteristics.

Sponsor: N/A

IRB/IACUC#: 2017-067
Effects of Practicing Osteopathic Manipulation Technique (OMT) on Hand Function

Purpose: Physicians who practice osteopathic manipulative treatment (OMT) rely on their hands to diagnose and treat patients. Due to the nature of medical practice, OMT practitioners’ experience increases as a function of age. Conversely, the general population’s hand function decreases with age, but skilled finger movement training improves an aging population’s hand functionality. Therefore, we hypothesize that OMT practitioners’ hand grip strength is maintained, or even improved, over untrained individuals within the same gender and age bracket in spite of increasing age.

Methods: 90 OMT practitioners at American Academy of Osteopathy’s 2017 Convocation self-reported demographic data via Qualtrics, such as age, gender, height, weight, and length of OMT practice. Then, we measured their intrinsic and extrinsic grip strength with a key pinch grip and Jamar dynamometer, respectively. Finally, participants allowed investigators to take photos of their hands with a ruler in-frame, so that anthropometric data including hand length and volume could be extrapolated.

Results: Preliminary data analysis shows that male OMT practitioners’ grip strength improves with age and that females’ decreases minimally. Other collected data is currently undergoing analysis and significance has yet to be determined. After factoring in subjects’ BMI and hand volume and comparing these values with accepted standards, we believe the data will show that OMT practitioners outperform their non-practitioner counterparts in extrinsic and intrinsic grip strength.

Conclusions: Our study paves the way for future tests in this population to determine if practicing OMT affects practitioners in quantifiable ways, such as increasing hand dexterity and tactile sensitivity.

Sponsor: N/A
IRB/IACUC#: 2017-043
Defining Muscle Energy: A Multidisciplinary Approach

Purpose: Manual manipulation is predominantly practiced among three professions: osteopathic medicine, chiropractic, and physical therapy. One treatment modality involves patients’ muscle contraction against practitioners’ counterforce. It is known as Muscle Energy Technique (MET) by osteopathic physicians, Autogenic Inhibition (AI) by chiropractors, and Proprioceptive Neuromuscular Facilitation (PNF) by physical therapists. Although these techniques involve the same principles, little is known about how each profession perceives and applies it to their practice. Understanding the approaches of each field can not only clarify patients’ past treatment histories but also yield opportunities for effective co-management. The objective of this project is to discuss the similarities and differences of this type of manipulative therapy.

Methods: Gathering and utilizing information obtained online and in written literature, this study compares treatment steps and applications of this form of muscle-based manual manipulation among osteopathic medicine, chiropractic, and physical therapy.

Results: Osteopathic MET – 1) Affected segment taken to restrictive barrier 2) Sub-maximal isometric contraction 3) Relaxation for 3-5 seconds 4) Segment taken to new restrictive barrier 5) Repeat 3-5 times Chiropractic AI – 1) Post-isometric Relaxation (PIR), which is identical to Osteopathic MET 2) Post-Facilitation Stretch (PFS): 2a) Maximal muscular contraction for 5-10 seconds 2b) Complete relaxation 2c) Rapid maximal stretch for 10 seconds 2d) Relaxation for 20 seconds Physical Therapist PNF – One continuous spiral motion of extremity in diagonal pattern via: 1) Passive range of motion 2) Active range of motion 3) Sustained isotonic contraction on full range of motion

Conclusions: Understanding these variations in technique maximizes its potential to be taken into a more comprehensive and advanced treatment modality that can be communicated and utilized by all three professions. This can augment the quality of manual medicine in patient care.

Sponsor: N/A
IRB/IACUC#: N/A
Evaluation of current educational methods incorporating Osteopathic Manipulative Medicine (OMM) into family medicine and internal medicine residency programs.

Purpose:

Osteopathic manipulative treatment (OMT) is one distinctive feature of osteopathic medical education and practice. Over the past two decades, multiple studies have cited concern over the decreased use of OMT by practicing osteopathic physicians [1, 2]. Some surveys of third- and fourth-year osteopathic medical students have shown that a majority of them intend to use OMT in their future practices [3, 4], but multiple surveys of practicing osteopathic physicians have shown low rates of OMT utilization in practice: over half of respondents used OMT for fewer than 5% of their patients; and 44% reported not using OMT at all [2, 5, 6]. Respondents indicated that their use of OMT in practice correlated with the extent of their clinical training, particularly during residency [2]. Therefore, the purpose of this study is to evaluate the barriers of OMT utilization by residents, and to determine potential changes needed in current and future osteopathic education to increase OMT’s use.

Methods:

A 28 question survey using the survey tool Qualtrix was sent to AOA and ACGME family medicine and internal medicine programs in the United States using an email link. Contacts of the programs coordinators and directors were obtained from public databases courtesy of the AOA and ACGME. Program contacts were asked to forward the survey link to the applicable residents (FM and IM residents only). Other residents that may have taken the survey unintentionally were excluded. Three reminders were sent via email 2 weeks apart. Participation was voluntary and participants could choose not to complete the survey without penalty. No incentive was offered for completion of the study.

Information received in this study was reported out in anonymous form only through the use of a generic hyperlink in the recruitment email that gave subjects access to the survey instrument. No names or personally identifying information was gathered through the survey. Only the named study investigators have access to the data.

Results:

(Data collection is still ongoing and final numbers may change.)

In the survey, 93% of Osteopathic respondents in the survey believed OMT to be an effective treatment for somatic dysfunction. However, out of these same respondents, 79% stated one of the barriers to preforming OMT on their patients was lack of time. Another large minority also noted lack of skill, and lack of supervision as obstacles.

Conclusion:
In conclusion, osteopathic education seems to be valuable in teaching the influence osteopathic manipulation may have. However, osteopathic educators may not be emphasizing how to incorporate OMT into the primary care setting. Therefore it may be beneficial to incorporate more case driven scenarios in undergraduate osteopathic education.

**Sponsor:** N/A  
**IRB/IACUC#:** #2017-150
PM&R Case Study: Neuropsychological Effects Following Traumatic Brain Injury

Background: According to the Center for Disease Control (CDC) close to 2.8 million people a year suffer from traumatic brain injuries (TBI) in the United States. Of that number, close to 96% will survive. The CDC estimates that medical costs as well as indirect costs, such as loss of productivity, nears almost 60 billion a year. With these staggering numbers, it is important to better understand the short term and long lasting effects of TBIs. TBIs can impair physical movement, vision, hearing, memory, thinking, and sensation. As well as cause depression and personality changes. Yet, some effects are less common such as verbal inhibition and emotional lability. Researching these unique cases can lead to better understanding of neuropsychology as well as better treatments to help those impacted.

Case Information: A chart review was conducted with the assistance of medical records, including clinical summaries, surgery notes, and long term rehabilitation records. A 53-year-old man suffered a motorcycle accident in March of 2011. During this accident, his helmet suffered major damage, he lost consciousness, and had a Glasgow Coma Score of 4. At the scene, he required resuscitation several times and was intubated. Once at the hospital he was diagnosed with multiple rib fractures, an open left calcaneus and fifth metatarsal base fracture, as well as a severe traumatic brain injury with intracranial hemorrhage. He was in a coma for 13 days and underwent several surgeries within the hospital. Once he was released he began to notice chronic daily headaches, greatly impaired sleep duration/quality, and chronic pain in the left foot/ankle. In addition, he began to suffer from an impaired memory, increased impulsivity, increased distractibility, emotional lability, anxiety, and an inability to censor his verbal speech. While his physical ailments have decreased his quality of life they have not been as severe as his neuropsychological changes. Before the accident he was able to work a high paying job. Yet, after the accident his inability to curb his speech, remember important items, and his greatly increased anxiety have caused him to no longer be able to work. In addition, he has difficulty going to the gym or the supermarket because he is unable to stop conversations with strangers. While he used to spend 45 minutes at the gym he will now spend close to 5 hours due to his ongoing conversations.

Conclusions: TBI is a major medical problem in the United States and while there can be great commonality among symptoms the ongoing sequela can be extremely varied. Yet, per the literature, there are very few cases on the loss of higher level filters on speech secondary to a TBI. Therefore, the specific mechanisms of this neurological injury as well as the ongoing rehabilitation and treatment are not well known. This case could provide an additional piece of the puzzle to potentially help advance the understanding of these rare long lasting effects as well as help provide a clearer picture of TBIs in general.

Sponsor: N/A
IRB/IACUC#: 2018-043
Psychosocial Difficulties in Pediatric Patients with Voiding Dysfunctions and Nocturnal Enuresis: Age and Sex-Related Differences

Purpose

To identify whether male and female patients presenting to a Pediatric Urology Voiding Dysfunction Clinic differ in terms of psychosocial difficulties.

Methods

A retrospective chart review was conducted to collect data from patients presenting to a pediatric urology clinic for voiding dysfunction or nocturnal enuresis between December 2016 and June 2017. During their visit, patients and their parents/guardians completed the Pediatric Symptom Checklist (PSC) and Dysfunctional Voiding Questionnaire (DVSS). Older children and teens also completed self-reports for the PSC.

Results

The sample consisted of 159 subjects (100 females, 59 males) between the ages of 5 and 16 years old (M = 9.86 + 3.15). Results revealed that children with more severe voiding symptoms exhibited more parent-reported attention (p=.019) and externalizing (p...

In a sex-based comparison, females self-reported significantly more psychosocial difficulties than males (17.81+1.9 vs 11.23+1.99; p=.03), while parents of males reported their children exhibited significantly more attention problems than females (4.14+.43 vs 2.94+2.67; p=.022).

Age- and sex-based comparisons revealed that for males, age was unrelated to any psychosocial difficulties. However, for females, older age was associated with more parent-reported psychosocial difficulties (p=.013) and internalizing problems (p...

Conclusion

Patients presenting to Pediatric Urology Voiding Dysfunction Clinics are at increased risk for psychosocial difficulties. Our data supports this finding, with more severe voiding symptoms being related to multiple aspects of poorer psychosocial functioning. Additionally, females are at increased risk for psychosocial difficulties, especially as they approach adolescence, while males are at increased risk for attention problems.

Sponsor: N/A
IRB/IACUC#: CCHCS-IRB
Epigenetic Evidence to Advance Utility of Lifestyle Interventions in Managing Depression in Primary Care Practice

PURPOSE: To evaluate and recommend lifestyle interventions as management for depression in primary care practice through systematic review of epigenetic evidence associated with depression.

BACKGROUND: Depression is the most common mental health condition in primary care patients in the United States. Compelling evidence shows that maladaptive lifestyle behaviors and environmental conditions are involved in the pathogenesis of depression via disease-promoting epigenetic mechanisms associated with depression in patients. However, lifestyle and environmental factors receive little consideration in current treatment of depression, while pharmacotherapy and psychotherapy are largely utilized. Therefore, considering utility of lifestyle interventions to alter gene expression associated with depression can provide a safe and low-cost option for prevention and treatment of depression.

METHODS: We performed a targeted and tailored search of peer-reviewed health science literature in MEDLINE through the PubMed interface. Through systematic review, we selected 34 articles that discussed epigenetic effects of depression as well as lifestyle intervention studies for depression. The search was limited to English language articles published in the last 10 years.

RESULTS: Our review consistently indicated that lifestyle modification efforts such as physical activity, anti-inflammatory foods, sleep hygiene, relaxation response, and social connectedness/group support serve as protective and therapeutic modalities for depression. Epigenetic evidence from our review confirmed that adverse lifestyle and environmental stimuli resulted in depression-promoting gene expression. Stress was found to be the most common risk factor for pathogenesis of depression. While few studies showed epigenetic evidence of lifestyle intervention approaches to depression management, relaxation response through meditation showed down-regulation of gene expression associated with stress and trauma that were evident to generally lead to subsequent depressive symptoms.

CONCLUSION: Understanding the epigenetic effects of lifestyle and environmental factors on development of depression are of considerable interest for understanding management of depression. While future study of epigenetic effects of multiple lifestyle interventions in depression management is needed, the present study may provide clinically relevant recommendations for using therapeutic lifestyle interventions in patients with depressive disorders in primary care practice, where epigenetic changes may serve as biomarkers for monitoring the course of illness. An epigenetics-based lifestyle intervention approach can aid in prevention and treatment of depression by motivating patients to change risky lifestyle and environmental factors that induce depression-promoting epigenetics.

Sponsor: N/A
IRB/IACUC#: N/A
Evaluation of Curriculum-Based Support Group (CBSG) Programs in Improving Psychosocial Behaviors in Kindergarten through 3rd Grade Students

Background. Tarrant County has the second highest number of confirmed abused/neglected children in Texas. Studies show maltreated children tend to develop poorly in certain psychosocial domains (i.e. confidence, cooperation, participation, decision-making, listening skills, peer interactions) which can affect academic performance, and mental health. Socioemotional learning programs in a classroom setting may mitigate such negative trajectories in ‘at-risk’ students by improving outcomes in these domains. The aim of this study is to evaluate curriculum-based support group (CBSG) programs in improving these psychosocial behaviors.

Methods. Secondary data analysis was conducted on maltreated or ‘at-risk’ maltreated children in kindergarten through 3rd grade (K-3). All races/ethnicities were included. Students attended small group sessions designed to enhance confidence, cooperation, participation, listening skills, appropriate interactions, and good decision-making skills. Pre- and post-program report card grades were used to measure improvement in math, reading, science and social studies. Psychosocial domains in the pre-, post, and 1-year post-program conditions were measured using a Likert Scale. Descriptive statistics and frequency distributions described the sample. Wilcoxon paired t-tests analyzed pre- and post-program improvement. Analysis of Variance (ANOVA) and Wilks Lambda with post-hoc corrections for multiple comparisons evaluated 1-year post-program follow-up. A 95% confidence interval (p= 0.05) was used.

Results. Participants (N=719) showed improvement in individual domains of: 36% confidence (t=10.29, p=0.0001), 28% cooperation (t=-10.89, p=0.0001), 26% participation (t=-8.38, p=0.0001), 26% listening skills (t=-9.57, p=0.0001), 31% decision-making (t=-9.27, p=0.0001), 24% peer interactions (t=-7.84, p=0.0001). Aggregated domains continued to improve 1-year post-program by 4.3% (t=-2.073, p=0.041) in a subset of participants (N=96). Academic performance also improved in a small sample of participants (N=24) by 8% in math, 7% science, 6.3% reading, and 5.3% social studies.

Conclusion. These data indicate that the CBSG program is effective at improving psychosocial behaviors in ‘at-risk’ children, and has the potential to mitigate negative trajectories up to a year. Evidence is encouraging that CBSG may also improve academic performance, although a larger sample size and control group is needed in future evaluations.

Sponsor: Recovery Resource Council
IRB/IACUC#: 2013-196
Does the Relationship Between Physical Activity and Mental Health Differ by Gender in Older Adults Who Have Had a Heart Attack?

Purpose: Post-MI adults are more likely to have depression and physical activity may help; however, there are limited findings for whether physical activity helps older post-MI adults, especially by gender. The purpose of this study was to analyze the relationship between physical activity and mental health in a general population of older adults (age 65 and older) who have had a heart attack and whether it differs by gender.

Methods: This cross sectional analysis used data from the 2015 BRFSS for males and females ages 65 and older who reported ever being diagnosed with a heart attack in Kentucky, Oklahoma, and West Virginia. Adjusted logistic regression analyses were conducted by gender to assess the relationship between physical activity and mental health while controlling for behavioral, health-related, and demographic factors.

Results: Across the states, 21-25% of adults 65 years and older who had experienced a heart attack reported poor mental health, and 40-47% reported being inactive. Adjusted analyses showed no significant relationship between physical activity and mental health, but did find activity limitations to be significantly related to mental health in females.

Conclusions: Overall, physical activity was not significantly related to mental health in general samples of men and women 65 and older who had been diagnosed with a heart attack. However, this study found an inverse relationship between activity limitations and mental health in females. Although physical activity should continue to be encouraged, clinicians should evaluate and screen older post-MI adults for activity limitations and mental health and vice versa, especially in females.

Sponsor: N/A
IRB/IACUC#: 2017-070
Parent’s Perception of Adolescents Health in Association with Child Reported Depression among Mexican American Children 10-14 Years of Age

Purpose: Depression in children is frequent and represents a challenge to be recognized by both the family and the primary care physician. Many parents are unaware of their child’s depression and may not recognize the symptoms, and primary care physicians do not routinely screen for depression in children. Providing a connection between the family, physician, and child to recognize depression is important. The purpose of this study was to examine the association between parent’s perception of their child’s health and child reported depression among Mexican American children 10-14 years of age.

Methods: One hundred and forty-four Mexican American children ages 10-14 and a parent/legal guardian participated in a cross-sectional study. Child participants completed depression screening using the child report Children’s Depression Inventory (CDI 2: Self-Report Short Version). Regression analyses were performed. Unadjusted and adjusted odds ratios and 95% confidence intervals were computed. The dependent variable was child report depression screening (average/lower and high average/elevated/very elevated), and the primary independent variable was parent reported perception of the child’s health (fair/poor or good/very good/excellent). The adjusted model controlled for family income, marital status of primary care giver, highest grade completed by anyone in the household, child age, and child gender.

Results: There were 74 (51.4%) male children, and the mean age was 11.97 (sd=1.45). Thirty (20.80%) of children screened high for depression, and parents reported fair/poor health for 11 (7.6%) of children. Children were more likely to screen high for depression if their parents reported their health as fair/poor [OR=11.85, (95% CI:2.65-53.05)] or if they were female [OR=3.58, (95% CI:1.37-9.35)] in the adjusted model.

Conclusion: Parents perception of their child’s health is associated with child self screening high for depression. Including a simple question about how a parent rates their child’s health could provide clinical utility for primary care physicians.

Sponsor: N/A
IRB/IACUC#: 2015-076
Does physical activity improve mental health in the older population aged 65 and older?

Purpose: Research has shown a positive relationship between physical activity and good mental health in most age groups; however, there is conflicting evidence about this relationship in the older population. The purpose of this study was to determine whether physical activity is related to mental health in the general population for those aged 65 and older.

Methods: This cross sectional analysis used data from the 2015 BRFFS for adults aged 65 and older from Alabama, Oklahoma and Oregon. The relationship between physical activity and mental health was analyzed using multiple logistic regression controlling for comorbid health conditions, depression, education, income, marital status, ethnicity/race, gender, and age.

Results: The majority of participants reported good mental health (74-78%); a moderate amount reported being highly active (32-51%), and less reported being insufficiently active (13-15%). In adjusted analysis, physical activity as well as depression were significantly related to good mental health in adults aged 65 or older across all three states.

Conclusions: Overall, physical activity is significantly related to good mental health in adults aged 65 and older. Females and those ever diagnosed with depression were less likely to report good mental health. When older adults present to primary care clinic, providers should screen their levels of physical activity and symptoms of depression. It is recommended that providers educate patients about the benefits of physical activity for mental health.

Sponsor: N/A
IRB/IACUC#: 2017-070
Personal, Psychological, and Family History Risk Factors for Emotional Eating Related to Obesity

Purpose: The concept that emotion strongly influences eating, referred to as “emotional eating” (EE), recently gained interest. Previous evidence suggested that overeating by overweight individuals reduces anxiety. The obesity literature indicated EE significantly differentiates obese from normal weight individuals. However, little is known about what other factors contribute to EE. This study aims to better understand risk factors that might be associated with EE. We anticipated that people with higher EE would be more likely to have family histories of anxiety or obesity, and would have more anxiety and stress, poorer coping skills, and higher BMI than people with lower EE.

Methods: Participants included adult men and women (n=97) with an average age of 30.78 years (sd=12.86) and an average BMI of 25.19 kg/m²(sd=5.69). Surveys included demographics, the State-Trait Anxiety Inventory to measure state ANX, and the Eating and Appraisal Due to Emotions and Stress to measure STR, EE, and COP. Subjects were categorized into higher and lower EE based on a mean split. Chi-square analysis was used to analyze differences in EE for FH of obesity and FH of anxiety. T-tests were used to analyze differences between high and low EE for ANX, STR, COP, and BMI.

Results: FH of obesity differed significantly by EE(x²=.009). Among high EE, 46.7% had a FH of obesity whereas among low EE 27.9% had a FH of obesity. FH of anxiety differed significantly by EE (x²=.045). Among high EE, 47.8% had a FH of anxiety whereas among low EE 28.0% had a FH of anxiety. When comparing individuals with high and low EE, state anxiety was higher for high EE (mean=36.09, sd=10.47) as compared to low EE (mean=31.28, sd=9.24) (t=2.41, p=.018). Stress was higher for high EE (mean=12.72, sd=3.11) as compared to low EE (mean=13.92, sd=2.89) (t= -1.98, p=.051). Coping was lower for high EE (mean=78.24, sd=8.57) as compared to low EE (mean=82.90, sd=9.21) (t= -2.57, p=.012). BMI was higher for high EE (mean=26.52, sd=7.02) as compared to low EE (mean=23.99, sd=3.87) (t= 2.22, p=.029).

Conclusions: EE is more likely with higher anxiety and poor coping skills. Additionally, a FH of obesity or anxiety appears to put individuals at risk for EE. Clinicians should be aware of the factors related to EE in order to identify patients who may be emotional eaters and provide targeted interventions in order to prevent obesity and promote weight loss.

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IRB/IACUC#: 2016-089
Gender Related Differences In Emotional Eating and Its Role In Obesity

Background: Obesity rates have increased and are linked to diseases such as cardiovascular disease, diabetes, and mortality, making it an important focus among health professionals. Current evidence shows that people who have high stress levels tend to be overweight and have higher rates of emotional eating (EE). To date, little is known about gender differences in EE. The purpose of this study is to analyze whether or not there are gender differences in EE and if it is tied to obesity.

Methods: 97 participants with an average BMI of 25.19kg/m² (sd=12.86) and average age of 30.78 years completed a self-report survey that assessed the participant’s level of stress and EE. Subjects were categorized into high and low EE based on a mean split, where lower values indicated a higher degree of EE. Chi square analysis was used to compare high and low EE by gender. Pearson correlation was used to determine association between EE and state anxiety for men and women. Independent samples t-tests were used to analyze differences in EE by BMI (normal weight versus overweight/obese) stratified by gender.

Results: Out of the 97 participants, 39% were overweight/obese. 56% were white/Caucasian, 28% were Asian, 8% were Hispanic, 8% were other. 54% were male and 56% were female. EE significantly differed by gender (x²=.001). Among women, 63.0% had high rates of EE. Among men, 27.9% had high rates of EE. Anxiety and EE were significantly correlated for women (p=.029) and men (p=.046). When comparing the overweight/obese individuals in each gender, EE was higher in overweight/obese women (mean=77.87, sd=19.98) as compared to normal weight women (mean=89.16, sd=14.84) (t=2.256, p=.028). There was no significant difference in EE between overweight men (mean=93.5, sd=15.86) and normal weight men (mean=98.63, sd=11.5) (t=1.168, p=.250).

Conclusion: More women than men reported EE. EE was higher in normal weight than overweight women but not between normal and overweight men. Clinicians should be aware of the factors related to EE in order to provide targeted interventions to prevent obesity and promote weight loss, especially in women who emotionally eat.

Sponsor: Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R25HL125447 to Dr. J.K. Vishwanath. The content is solely the responsibility of the authors

IRB/IACUC#: 2016-089
Temperature Regulated Cooling Wheelchair Design and Testing for Pressure Ulcer Prevention

Background: Long-term wheelchair users are prone to developing pressure ulcers due to complications including reduced mobility, impaired sensations from neurological insults, vascular problems, decreased cognition, and morbid obesity. Pressure ulcers are wounds that result from breakdown of tissue over bony prominences due to localized ischemia caused by constant pressure. The compromised blood circulation along with reduced airflow results in an accumulation of heat in the tissue over the bony prominence that accelerates tissue breakdown. Current ulcer preventing wheelchairs employ thick, foam cushions, which distribute and reduce pressure, but also lead to poor heat distribution contributing to the risk of developing pressure ulcers.

Purpose: In this study, we designed a custom-built cushion that circulates chilled water. We measured buttocks surface temperatures and peak pressures around the pelvic bones, with a targeted maximum temperature and pressure of 28°C and 60mmHg, respectively.

Method: In this ongoing study, we recruited three subjects who were asked to sit and operate a motorized wheelchair with the aforementioned cushion for 30 minutes. Thermal images of participants buttocks were taken before and after wheelchair use by an Infrared (IR) thermal camera (Flir, T650sc). Temperatures of buttocks (coccyx, right and left thighs proximal to ischial tuberosities), circulating water and ambient were acquired about every second while seated, using digital thermometers (DS18S20) via a microcontroller unit (Arduino Uno). Pressure distribution was captured at the end of the wheelchair use using a pressure mat (Tekscan ConforMat), which was placed on top of the cooling cushion.

All study procedures were approved by the institutional review board (IRB) prior to recruitment and testing, and informed consent was obtained from subjects prior to testing.

Results: The results indicated that the cooling cushion was capable of cooling tissue from 27.9 to 24.9°C in 30 minutes. The circulating water temperature was 21.8(0.3)°C while ambient temperature was 22.3(0.5)°C. Peak pressure occurred at the right ischial tuberosity in all subjects and was quantified as 92(5)mmHg while average pressure was around 60mmHg.

Conclusion: The custom-built cooling cushion maintained temperatures of the buttocks below 28°C, but failed to lower the peak pressure to below 60mmHg. Further modifications such as an additional comfort layer and a longer duration testing of the design are warranted to achieve our goals.

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Retraining Sensory Weighting Using Virtual Environment and Vibrotactile Biofeedback

Purpose: The aim of this study was to evaluate the effectiveness of a balance rehabilitation protocol to retrain the sensory weighting mechanism by utilizing vibrotactile feedback and training in virtual environment (VE).

Materials/Methods: 20 participants, 10 non-diabetic young adults (NDYA) and 10 diabetic older adults with peripheral neuropathy (DAPN).

We experimentally induced somatosensory loss in NDYA with inflated pressure cuffs on the ankles for 35 min and then placed a vibrotactile system with low and high frequency stimulation. Data was collected at baseline and during the last 15 minutes of the ischemic protocol under three conditions: no vibration, low frequency and high frequency vibrations. Outcome measures included center of pressure (COP) variability, plantar surface pressure sensation and vibratory threshold.

The DAPN participated in 6 (1-hour) training sessions with visually engaging VE which progressively challenged walking and balance tasks. Vibratory devices were placed around ankles, above the level of sensory loss, delivering constant sub-threshold white noise stimulation. In visits 1 and 8 pre- and post-training functional assessments of balance and gait function were conducted.

Results: In NDYA, ischemia increased COP variability and plantar surface pressure sensation threshold (p=.01 and p = 0.3 respectively) and decreased the vibratory extension threshold measured at the hallux IP joint (p) during CTSIB for eyes closed conditions both on stable and foam surface (p

Conclusions: The vibratory biofeedback was able to partially compensate for the experimental induced sensory loss and improve balance function in healthy young adults. Results of the training protocol suggest support for the stochastic resonance theory and show that sensory retraining in VE and vibratory device is feasible in diabetic subjects holding promise for improvement of function due to an increased ability to integrate all sensory inputs available and a decreased reliance on visual inputs.

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IRB/IACUC#: 2012-007
A Systematic Review of Physical Therapy Interventions for Parkinson’s Disease

Purpose: The purpose of this systematic review is to identify effective interventions applied by physical therapists to address common impairments in patients with Parkinson’s Disease (PD).

Methods: A search of Pubmed, Medline, Scopus, Wiley Online Library, EbscoHost, CINHAHL were used to identify studies published from 2007 to 2017 written in English with the key words: Parkinson’s Disease, posture, balance, gait, rigidity.

Results: 25 studies published between 2007 to 2017 that met the inclusion criteria were used. Based on the quality level of evidence, 13 of the studies were qualified as IB, two as IIB, and 10 as III. To address posture, using a hyperextension brace while performing strengthening exercises for 30 minutes a day for four months, strengthening while wearing a weighted backpack twice a day for five weeks, or a multiple intervention approach that incorporates functional strengthening for five days a week in a four-week period can be beneficial. Usage of an UpRight device for 21 consecutive days or kinesio tape with postural rehabilitation in 12 visits over four weeks can be incorporated. Use of aquatic rehabilitation can be used to treat abnormal flexion when completing five sessions per week for a total of eight weeks. To address rigidity, Yoga can be beneficial when performed two times a week for 12 weeks. Interval training three times a week for eight weeks can decrease rigidity. Treatments for gait include LVST BIG four times per week for four weeks. A curved walking program for 12 sessions over four to six weeks can increase gait speed. Auditory cueing during the first month of gait training and progressive resistance training can be incorporated two times a week for 10 weeks. Such improvements include decreasing freezing of gait, increased stride length, and speed of movement. To address balance impairments, Tai Chi can be done for two to three times a week for 60 minutes, dance therapy for 75 minutes, Adaptive Tango twice a week, or Argentine Tango can be performed five times a week. Repetitive step training three times a week or HiBalance training three times a week can improve balance.

Conclusion: This review indicates that multiple approaches can be used to treat common impairments such as posture abnormalities, rigidity, balance and gait deficits seen in patients with PD.
**Does Cognitive Restructuring Improve Postural Control in Older Adults?**

**Purpose:** Falls are a major source of disability in the aging population. The cause of falls is multifactorial, but components such as fear of falling are often overlooked. Older adults that have a fear of falling also have an increased risk for future falls. Physical therapists use cognitive-behavioral therapy techniques such as cognitive restructuring, to enhance treatment and reverse the fear of falling. However, there is a paucity of evidence regarding the effects of cognitive restructuring on postural control. The purpose of this investigation was to determine if an 8-week cognitive restructuring program, designed to reduce the fear of falling, can improve postural control in older adults.

**Methods:** 4 healthy older adults (avg age 73.3 ± 8.5 yrs) who passed a screening test underwent postural control testing before (T0) and after (T1) an 8-week cognitive restructuring program. Clinical balance testing included the Activities-Specific Balance Confidence (ABC) Scale, Timed-Up and Go (TUG), and Four Square Step (FSST) tests. The experimental balance testing included static and dynamic balance using a 12-camera Motion Analysis system that tracked markers on the body for calculation of temporal and spatial kinematic movements. A V-GAIT CAREN system with dual-belt treadmill motion platform was used to create perturbations to balance. Paired samples t tests were used to compare before and after variables of each of the clinical and experimental tests. Significance was set at p < 0.05. All analyses were performed using SPSS.

**Results:** Clinical balance testing of the ABC (p=.672), TUG (p=.179), and FSST (p=.748), found no statistically significant differences. Statistical significance was found for experimental testing of dynamic backward-directed balance perturbations in two phases. The center of pressure-center of mass difference (COP-COM) was significantly increased at 1/3rd (p=.003) and 2/3rd (p=.009) of the recovery step from before (T0) to after (T1). The mean difference in scores was -.014mm for 1/3rd, -.027mm for 2/3rd, and -.065mm for 3/3rd of the recovery step.

**Conclusions:** Experimental testing showed significant increases in COP-COM in two of three phases of stepping and approached significance for the complete task. Large differences in COP-COM are indicative of robust postural control. Our results demonstrate that a cognitive restructuring program can improve stability and control over falls in older adults.

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**IRB/IACUC#:** 2014-139
Impact of High Intensity Aerobic Exercise on Aging-Related Motor Function Changes

Purpose: Impairments in motor function are predictive of adverse health outcomes including increased mortality and disability. This study investigated the longitudinal impact of high intensity aerobic exercise on motor function impairment associated with aging. Effects on baseline heart function were also evaluated.

Methods: Subjects completed motor function testing including a grip strength test using the Hydraulic Hand Dynamometer, the 6-minute walk test (6MWT), responses to unexpected balance perturbations delivered by surface translation in anterior Posterior direction, and self-selected gait speed. These motor function tests were administered at baseline, 1-2 months post-baseline, and 3-4 months post-baseline at the end of exercise training. Subjects were randomly assigned to an exercise or non-exercise group. The exercise group completed 36, 1-hour exercise sessions, 3 times a week over 3-4 months. Exercise was standardized for each subject and consisted of a 10-minute warm-up (range of motion exercise, walking, stretching), followed by a fast pace walk/jog on a treadmill for 40 minutes, and concluded with a 10-minute cooldown. A high intensity exercise at 80% max heart rate was aimed for as long as possible in each session. Exercise intensity was progressively increased over the weeks of training. Heart rate, blood pressure and oxygen levels were monitored throughout the exercise sessions. Data was analyzed and compared between the groups of subjects with repeated measures ANOVA

Results: Preliminary results from the exercise subject, show improvement in motor function, increased self-selected gait speed and endurance (6MWT) at the mid-point and at the end of exercise regime. There were no effects on grip strength or balance control measures. Compared to baseline values, after exercise training, average resting heart rate and blood pressure measurement decreased significantly from 88 bpm, 138/89 to 75 bpm, 124/80 respectively.

Conclusion: A program of sustained, high intensity aerobic exercise, at the upper limits of currently prescribed maximum heart rate is feasible in middle age and older individuals without adverse effects. Improvements in gait speed, endurance and heart function are promising.

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IRB/IACUC#: 2016-140
Variation of Posterior Deltoid Muscle

Background: Shoulder anatomy develops into a complex structure with some of the widest ranges of motion displayed on the human body. Held together entirely by ligaments and muscles, the shoulder a relatively weak joint with many clinical presentations. An overlooked attribute is the anatomic variability within the shoulder region. During a routine dissection, bilateral Posterior variants of the deltoid muscle, with an interesting orientation of muscle fibers, were discovered on a 78-year-old female cadaver. These variants show an almost perpendicular orientation to the expected direction of deltoid muscle fibers and are not consistent with any other expected muscle bellies in the region.

Case Information: While performing a routine dissection in the gross anatomy laboratory, aberrant deltoid muscle straps were observed bilaterally on a 78-year-old female cadaver. These fibers, seen in the figures below, extend superficially from the lateral aspect of the overlying deltoid and lateral triceps brachii fascias. These fibers then lay on top of the infraspinatus muscle belly. Directionally they run at a perpendicular angle to the Posterior deltoid fibers and are contained within a separate fascial sheath lying superficially over the existing muscle bellies. An additional, albeit rather small, set of fibers run from the same deep deltoid and triceps brachii fascias to then lay over the scapular spine origin of the Posterior deltoid. Although these fibers are contained within a separate fascial sheath, there appears to be no change in the neurovascular anatomy associated with the Posterior shoulder. A separate neurovascular bundle was not noted to accompany either of the variant muscle straps.

Conclusions: Aberrant straps of muscle in the deltoid region have been described on several occasions. The shoulder joint is an unstable joint with one of the widest ranges of motion of any joint in the body. Its mobility is derived from the construction of the capsule, which is composed of a network of tendon and connective tissue. Consequently, this joint is the source of a great number of acute and chronic pain cases. Perhaps a portion of these cases may be attributed to the presence of variant muscles influencing the shoulder joint. In addition to pain, the shoulder is a frequent location for a variety of surgical procedures. Effective clinical management of patients with concerning shoulder issues should include consideration of atypical structures, whether intra-operatively or not.

Sponsor: N/A
IRB/IACUC#: N/A
Bronchopulmonary Variation in a Case of Situs Inversus Totalis

Background: Situs inversus totalis is the transposition of thoracic and abdominal internal organs across the sagittal plane. The incidence of situs inversus totalis is 1:10,000. This case of situs inversus totalis had variant bronchopulmonary laterality. Through extensive literature review we report no other documented cases of individuals with this anatomical variation.

Case Information: This study involved detailed dissection of a 71-year-old male with situs inversus totalis and variant bronchopulmonary structures. This study serves to add to the expanding body of knowledge of situs inversus totalis and variations from the expected laterality. In the expected anatomy of individuals with situs inversus totalis, the right lung is bi-lobed and the left lung is tri-lobed. However, this case is exceedingly rare in that the individual maintained a tri-lobed right lung and bi-lobed left lung. In contrast to this, the cadaver maintained the expected situs inversus laterality of both hilar structures. The cadavers tri-lobed right lung maintained the pulmonary artery superior to the primary bronchus while the cadavers bi-lobed left lung possessed the pulmonary artery anterior to the primary bronchus. All other visceral findings were consistent with the expected laterality.

Conclusions: As the cadaver maintained expected laterality of the bronchi and pulmonary arteries but did not maintain expected lung structure, we suggest that these findings may assist current research in determining the specific point in embryological development that laterality is determined. Clinicians, surgeons and radiologists should be aware of situs inversus totalis for diagnostic and therapeutic procedures and current clinical guidelines should take these rare variations into consideration.

Sponsor: N/A
IRB/IACUC#: N/A
MASSIVE RIGHT-SIDED HIATAL HERNIA VARIATION: A Case Report

Background: A hiatal hernia describes a herniation of abdominal contents, typically the stomach, through the esophageal hiatus into the mediastinum. The majority of reported paraesophageal hernias (PEH) are left-sided; although, right-sided hiatal hernias have a better prognosis, there is little mention of them in current literature.

Case Information: During a routine cadaver dissection for academic purposes, a massive hiatal hernia was identified in an 84-year-old female. This anatomic variant case presents with the abdominal contents of the entire stomach, pyloric sphincter, and portions of the greater and lesser omentums displaced into the right thoracic cavity. Such hernias can have acute symptoms, chronic symptoms, or present as asymptomatic. In this case report, the donor was thought to have no significant functional abnormalities, although there were reports of gastrointestinal bleeding.

Conclusions: We believe this case to be a rare variant due to two factors: the size of the hiatus, and the displacement of the hernia into the right side of the mediastinum. The hiatal surface area (HSA) in this case report was calculated to be $17.41\text{cm}^2$, which is almost three times the established average HSA in normal patients. This case report attempts to add to the body of literature detailing right-sided hiatal hernias. Looking forward, we believe that there is great scope for future research specific to right-sided hiatal hernias and improvement in the quality of life for those who undergo elective PEH repair.

Sponsor: N/A
IRB/IACUC#: N/A
Validating the Pig ACL as a Model for Pre-Clinical Testing of Ligament Repair Techniques

Purpose: Advancements in surgical repair and reconstruction of the anterior cruciate ligament (ACL) necessitate an appropriate animal model for pre-clinical testing. Furthermore, pre-clinical testing using cadaveric tissue is less readily available and comes at a greater cost as compared to animal tissue. Although the literature suggests the use of a pig model as a good biomechanical alternative for knee joint studies, only a limited number of studies have investigated similarities in knee joint anatomy. This study specifically aims to establish a method for comparing the geometric length, width and thickness of the ACL between humans and pigs in an effort to provide a measurement of proportionality between the two. Although the pig ACL may be smaller in overall size, we hypothesize that the dimensions will be proportional. Developing a repeatable measurement method and understanding geometric differences can help in study design (e.g., selecting suture size for ligament repair), control for experimental variation, and adds to our understanding of the mechanical differences that may be observed during testing. Although this is a preliminary study, future studies expanding this work will help determine if the pig is an appropriate alternative. Projecting ahead, as these examinations advance into in vivo studies, a validated pig model can serve as a way to follow long-term outcomes.

Methods: Multi-planar digital images were acquired of a sectioned anterior cruciate ligament (ACL) from both a juvenile Yorkshire pig and a 78 year old male cadaver. Each image was imported and calibrated using imageJ (1.49v, National Institutes of Health, USA). Measurements were taken by two independent observers to determine ACL length, width, and thickness for comparison between human and pig ACL dimensions. A paired t-test was performed to establish inter-observer image measurement reliability (alpha=0.05).

Results: No significant difference between readers was found in the ACL dimensions measured (p=0.23). The pig ACL had a length of 25.9-mm, a width of 10.6-mm, and a thickness of 4.1-mm. The length and thickness of the pig ACL were both 24% smaller than the human ACL. The width however did not match the scaling factor found in the other two dimensions resulting in only a 14% decrease as compared to the human ACL.

Conclusions: This preliminary study establishes a reliable method for measurement of ligament dimensions. Although limited in sample size, the comparison between the ACL of a Yorkshire pig and a human was found to be proportional in two of the three dimensions studied. Moreover, visual comparison showed the ligaments to have very similar planar geometries. The study is currently ongoing and more samples are being collected and analyzed. Such geometric information will help add to our understanding of the ACL as a structure and add to the biomechanical tissue data available in the literature. Moving forward, we hope to use the pig as a model to study two novel ACL repair techniques.

Sponsor: N/A
IRB/IACUC#: 2017-0029
Thermoregulation and the Human Nose: Balancing Climatic and Energetic Factors

Purpose: Studies have shown that indigenous individuals from cold-dry climates exhibit longer, taller, and especially narrower nasal passages compared to equatorial counterparts, enhancing inspiratory air-conditioning (heating and moisturizing) capacity and reducing susceptibility to respiratory tract infections. Concurrently, due to increased demand for thermogenesis, cold-dry climates are also metabolically more expensive than tropical environments, necessitating greater volumetric intake of oxygen. Accordingly, recent research has suggested that while a narrower nose enhances inspiratory air-conditioning, the accompanying restriction on volumetric intake may necessitate increased nasal height to maintain sufficient intake of oxygen. The purpose of this study was to examine the relationship between nasal dimensions, climate, and the metabolic demands.

Methods: We employed 12 linear measurements collected from the nasal skeleton of 837 modern human crania from major geographic (Arctic Circle, Asia, Australia, Europe, Africa) and climatic (polar, temperate, hot-arid, tropical) zones. Anterior-Posterior femoral head diameter (FHD) was further employed as a proxy for overall body size and metabolic requirements. Morphological, climatic, and geographic data were then employed in multivariate analyses.

Results: Our results indicate that most breadth measurements of the nasal aperture and internal cavity are significantly correlated with climate (all significant $R^2$ values between 0.29–0.51 with p-values < 0.004), but not FHD. Conversely, height and length measurements of the aperture and cavity were found to be more strongly correlated with FHD (all significant $R^2$ values between 0.67–0.78 with p-values < 0.0003) compared to climate (all significant $R^2$ values between 0.36–0.56 with p-values < 0.02). Further, overall nasal passage area was found to be positively associated with FHD ($R^2 = 0.67$, p = 0.0003), while nasal passage shape retained a significant relationship with climate ($R^2 = 0.66$, p = 0.0004) with relatively tall/narrow airways associated with colder-drier environments.

Conclusion: Collectively, these results support the assertion that physiological demands for temperature and moisture exchange are predominantly mediated by nasal passage breadth, with airway height representing a compensatory mechanism for ensuring a metabolically sufficient oxygen intake. Additional studies employing more direct measures of metabolic demands are accordingly warranted.

Sponsor: N/A
IRB/IACUC#: N/A
The Craniofacial Phenotype in a Mouse Model of Osteogenesis Imperfecta

Purpose: Osteogenesis Imperfecta (OI, or “brittle bone disease”) is a rare disorder that is caused by genetic point mutations (COL1A1/COL1A2) that affect type 1 collagen. In OI type III (severe) patients, limb bones are more susceptible to skeletal fractures and the bones of the craniofacial region are underdeveloped. Some OI type III patients also suffer from dental malocclusions or fractures (dentinogenesis imperfecta). The goal of this project is to describe the facial phenotype in an OI mouse model, to see if this model can be used to test potential behavioral and pharmaceutical interventions.

Methods: The homozygous OI murine (OIM−/−), a mouse strain with a nonlethal recessively inherited mutation of the COL1A2 gene, is a potential model for the human OI type III. OIM−/− and wild type (WT) littermates were raised from weaning (21 days) to adulthood (16 weeks). Digital 3D craniofacial landmarks were taken from in-vivo micro CT scans, and Kuskal-Wallis ANOVAs (α=0.05) were used to compare centroid size and interlandmark distances between genotypes.

Results: Adult OIM−/− mice were found to have decreased cranial and mandibular centroid sizes, compared to WT mice. OIM−/− mice also show several morphological similarities to the OI type III human phenotype, such as shortened basicrania, facial hypoplasia, and altered dental spacing.

Conclusions: We conclude that this mouse model shows potential for future investigations of the growth mechanisms underlying the craniofacial presentation of OI. Subsequently, we will next explore the possibility of using increased masticatory loading during the early growth period to stimulate craniofacial bone growth and improve bone quality in the OIM mouse model.

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IRB/IACUC#: Indiana University School of Medicine 11133
Establishing Experimental Sample Uniformity Prior to Patella Component Fixation Testing

Purpose: It is imperative to perform quality control studies to validate experimental sample quality prior to testing. Due to the inherent inconsistency when using cadaveric bone as a means to test clinically relevant hypotheses, one such quality check is to geometrically study the variability present in the bone samples. Thus, as a quality control step prior to investing resources to undertake the overall aim of studying patella component fixation in total knee arthroplasty (TKA), this study aims to establish sample uniformity by analyzing patella length, width, and depth.

Methods: Ten random pairs of patellae were harvested from a possible 39 embalmed cadavers. Each patella was then prepared by an orthopaedic surgeon, as if performing an intraoperative TKA, for fixation of a patella implant component. After preparation but before adding a patellar component and cement, the surgeon visually inspected each patella and separated each pair with the better bone quality sample as part of the control group and the other as part of the treatment group. Measurements were then taken by two independent observers using a caliper to determine the superior-inferior patellar length (SIL), medial-lateral width (MLW), and the sectioned patellar thickness (TH). T-tests were performed to establish interobserver measurement reliability and the geometric uniformity between the control and treatment groups and between the left and right samples.

Results: There was no significant difference between readers in the SIL (p=0.48), MLW (p=0.58) and TH (p=0.23) measurements. No significant differences were found when comparing between the control and experimental groups for any of the three measures (SIL p=0.21, MLW p=0.44, TH p=0.90). There was however, a significant difference observed in the sectioned preparation TH (p=0.007) when comparing left and right knee patellae.

Conclusions: Based on the geometric outcomes measured (SIL, MLW, TH) the results of this study validate the sample uniformity when comparing patellae based on control and treatment groups rather than right verses left. Doing so helps control sample quality for completing the overall aim to study cement fixation methods of the patellar component in TKA.

Sponsor: N/A
IRB/IACUC#: N/A
Sexual Dimorphism in the Trochlear Angle of the Humerus: A preliminary investigation in Hunter-Gatherers and Agriculturalists

Purpose: Previous research has argued the elbow “carrying angle” to be sexually dimorphic in humans, with females exhibiting greater abduction of the supinated forearm at full extension. Moreover, it is generally assumed that the trochlear angle of the humerus is the primary skeletal basis of the carrying angle, and thus, may independently provide a reliable osteological indicator of sex in forensic, bioarchaeological, and paleoanthropological contexts.

Methods: Here, we employed the software TPSDig2 to derive trochlear angles from photographs of humeri collected on 40 (17 female/23 male) adult Archaic-period Amerindian hunter-gatherers and 54 (24 female/30 male) adult Medieval European agriculturalists. Due to handedness, angles from left and right humeri were averaged for each individual, with asymmetry assessed by subtracting the more acute angle from the more obtuse angle irrespective of actual left/right siding.

Results: Although based on small sample sizes, males and females were not found to be significantly different from each other in either the Amerindian (t=1.5, p=0.13) or European (t=-1.3, p=0.26) samples. With both sexes pooled, the Amerindian sample exhibited more acute trochlear angles (t=4.64, p < 0.0001) and greater bilateral asymmetry (t=-2.07, p=0.042) than the Europeans. Additionally, although not statistically significant, Amerindian males (bilateral difference μ=5.92°) were found to be more asymmetrical than Amerindian females (μ=4.65°), while asymmetry values in European males (μ=3.69°) and females (μ=3.63°) were virtually identical.

Conclusions: While failing to support the trochlear angle as a diagnostic sex indicator, our results are consistent with previous research generally demonstrating elevated levels of upper limb asymmetry in hunter-gatherer populations — asymmetries typically attributed to reliance on activities requiring greater unilateral loading of the dominant limb. Accordingly, the results of this study may indicate that more acute trochlear angles (less forearm abduction) reflect higher levels of biomechanical loading. Thus, sexual dimorphism in the carrying angle, if/when present, may be dependent on sex-specific activity patterns.

Sponsor: Benjamin A. Gilman International Scholarship

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Diagnostic Validation of Dynamic Ultrasound Evaluation of Supination-External Rotation Ankle Injuries

Purpose: Definitive diagnosis of syndesmosis injuries can be made with plain film radiographs if the injury is severe enough, but often is missed when severity or image quality is low. Ultrasound diagnosis may circumvent many of these disadvantages by being inexpensive, efficient, and able to detect subtle injuries without radiation exposure. This study evaluates the ability of ultrasound to detect subtle SER ankle syndesmosis injuries with a dynamic external rotational stress test.

Methods: Nine male fresh frozen specimens were secured to an ankle rig and stress tested to 10 Nm of external rotational torque with ultrasound monitoring at the tibiofibular clear space. The ankles were subjected to syndesmosis ligament sectioning and repeat stress measurements of the tibiofibular clear space at peak torque.

Ankle States Examined:
1. Intact State
2. 75% of AITFL Cut
3. 100% of AITFL Cut
4. Fibula Fx - Cut 8 cm proximal
5. 75% PITFL Cut
6. 100% PITFL Cut

Results: Dynamic external rotation stress evaluation using ultrasound was able to detect a significant difference between the uninjured ankle tibiofibular clear space of 4.5 mm and the injured ankle with 100% of anterior inferior tibiofibular ligament cut 6.0 mm (P=.017). Additionally, this method was able to detect significant differences between the uninjured ankle and the injured states.

Conclusion: Dynamic external rotational stress evaluation using ultrasound was able to detect stage 1 Lauge-Hansen SER injuries with statistical significance and corroborates criteria for diagnosing a syndesmosis injury at ≥ 6.0 mm of tibiofibular clear space widening.

Sponsor: N/A
IRB/IACUC#: N/A
Surface projection of the Posterior interosseous nerve and artery as they exit the supinator and interosseous foramen respectively: A cadaver study

Purpose: The purpose of this study was to develop a method for locating surface projections of the Posterior interosseous nerve (PIN) and Posterior interosseous artery (PIA) as they exit the supinator muscle and interosseous foramen respectively.

Methods: Distances from the vertical and transverse planes through the lateral epicondyle of the humerus to the exit point of the PIN through the supinator and the PIA through the interosseous foramen were measured on 10 upper extremities from 5 cadavers. Average distances were used to find coefficients in terms of the thumb interphalangeal joint widths.

Results: The mean transverse plane distance from the lateral epicondyle to the exit points of the PIN and PIA were 79.38 mm (~4.0 IPJ widths) and 90.62 mm (~4.5 IPJ widths) respectively. The mean vertical plane distance from the radius to the exit points of the PIN and PIA were 9.45 mm (~0.5 IPJ widths) and 10.86 mm (~0.5 IPJ widths) respectively.

Conclusions: The results of this study present a method to assist clinicians in avoidance of iatrogenic outcomes with the application of various treatments such as dry needling and acupuncture.

Sponsor: N/A
IRB/IACUC#: N/A
Variation of Median Nerve Pathway Around the Elbow Joint

Introduction

The median nerve is one of the large terminal branches originating from the brachial plexus. It provides the motor innervations to both the forearm and palmar hand, as well as most of the sensory innervation for the palmar hand. On the way to its targeted areas, the median nerve pathway from the upper arm to the hand may pass through some muscles and other accessory structures that may not be considered normal, particularly around the elbow area. The purpose of this study was to trace and observe how this nerve travels in terms of the relationship with surrounding structures proximally and distally to the elbow.

Methods

Twelve upper extremities from six cadavers (3 males and 3 females) were dissected to trace and observe how the median nerve travels in these specimens. The focused area was from the middle upper arm to the proximal 1/3 of the forearm.

Results

All twelve identified median nerves passed between the biceps brachii and brachialis muscles. In ten out of the twelve specimens, about two to three fingers width proximal to the elbow joint line between the medial and lateral epicondyles of the humerus, it was found that the median nerve surfaced from the inferomedial edge of the biceps muscle and continued traveling down under a tight bicep aponeurosis and then pierced into the pronator teres muscle - common impingement areas for the median nerve. After we reflected the biceps muscle laterally from the remaining two of the twelve left forearms to expose the median nerve, it was observed that the nerve pierced through the brachialis muscle at its superior border (three to four fingers width proximal to the joint line), which was a very interesting finding. The nerve exited from the inferior border of the muscle, continued to pass down for one to two fingers width, and pierced the pronator teres as did the other ten median nerves.

Conclusion

Observing two of twelve specimens, the median nerve showed a different pathway around the elbow joint, which is abnormal from others’. Namely, the nerve pierces through the brachialis muscle before descending and passing through the pronator teres muscle.

Clinical Implication
Such a variation of the median nerve pathway has not been reported before. This finding may offer clinicians an additional explanation of the median nerve impingement-related clinical symptoms that are very similar to the pronator teres syndrome.

Sponsor: N/A
IRB/IACUC#: N/A
She's Healthy and Empowered: Optimizing Social Network and Improving Health

Purpose:
Developed through community-based participatory research (CBPR) approach, SHE Tribe aims to promote healthy lifestyles among women. The program encourages women to utilize their supportive social networks and work towards making meaningful behavior changes through five program gatherings. During each gathering, a peer facilitator motivates their tribe to set individual goals, do actions needed to achieve those goals, and reflect on factors that may aid or hinder successful completion of those goals. The purpose of this study was to assess changes in the overall well-being of SHE Tribe participants.

Methods:
Participants were asked to complete a baseline assessment before commencing the program followed by a post-assessment upon completion. The questions included in the assessment package were utilized to generate customized feedback on five health domains: me (general well-being), mind (mental health), matter (what we consume), move (physical activity), and meet (social support). To standardize the measurements, the total score for each domain was converted into a 100-point scale. Paired t-tests were conducted to assess change in the respective areas of health before and after participants’ enrollment in the program.

Results:
A total of 39 women have enrolled in the program. Among 29 women with complete pre-post data, 93% showed improvement in at least one of the five domains. Additionally, 90% displayed progress in two or more domains and 55% enhanced more than three areas of their health. Paired t-tests showed significant improvement in areas such as me, mind, move, and matter (p < 0.05). There was a slight improvement in the meet category as well. However, the change was not statistically significant.

Conclusions:
SHE Tribe participants showed improvement in several areas of health. This study highlights the success of a social network based peer-led model in empowering women and promoting healthy lifestyle choices. Furthermore, programs fostering intrinsic motivation and self-efficacy such as SHE Tribe show promise with improving health.

Sponsor: N/A
IRB/IACUC#: 2016-121
Voluntary Blood Donations: A Path to Adequate Blood Supply and Fewer Maternal Deaths in Nigeria

Purpose

Maternal mortality in Nigeria represents a substantial fraction of the burden of pregnancy-related deaths globally. Obstetric hemorrhage is a major cause of maternal death in Nigeria. The prompt transfusion of safe blood could save many women with obstetric hemorrhage. The World Health Organization (WHO) recommends national blood bank systems that are exclusively supplied by voluntary donors. Blood donors in Nigeria include relatives of transfusion recipients, commercial suppliers, and altruistic donors. This review examines global experiences with blood donation and the applicability of WHO recommendations in Nigeria for improved maternal outcomes.

Methods

The WHO recommendation for voluntary blood donation and its justification were examined in scientific literature and grey literature. The search terms ‘blood donation,’ ‘voluntary,’ and ‘Nigeria,’ were used in PubMed to locate 24 publications spanning the last 10 years. Successful experiences with WHO recommendations in 4 developing countries were reviewed. An analysis of Nigerian studies was conducted to identify prevalent attitudes and practices related to blood donation.

Results

The WHO recognizes voluntary blood donations as a viable means of collecting safe blood for clinical use. Nicaragua, Iran, and China are developing countries that have recorded notable success with blood systems exclusively supplied by voluntary donors. Between 2002 and 2016, in the African country Mauritius, total blood supply increased as the proportion of voluntary donations rose from 60 to 82.5%. Despite a good level of knowledge that could facilitate blood donation in certain segments of the Nigerian population, voluntary donations are unsatisfactory. Nigerians with a favorable attitude to donation report inadequate opportunities and a lack of prompting. Additional barriers to voluntary donations in Nigeria could be classed into the categories of fear and policies. Potential donors report fear of needle pricks, negative health effects, HIV detection, and the inappropriate use of donated blood. A policy environment that is insufficiently supportive of blood donations is reflected in absent legislation.

Conclusion

A national blood bank system underpinned by voluntary donations is desirable and achievable in Nigeria. Strategic leadership, education that dispels fears surrounding blood donation, infrastructural investments, and collaborative partnerships with domestic and international stakeholders are required for improvements in Nigeria’s blood transfusion system. By improving the availability of safe blood for transfusion, the burden of maternal deaths in Nigeria could be reduced.

Sponsor: N/A
IRB/IACUC#: N/A
A Case of Ovarian Torsion in the 3rd Trimester of Pregnancy

Background

Ovarian torsion is a rare occurrence during pregnancy, especially in the third trimester. It is a gynecological emergency and needs to be promptly reversed in order to preserve ovarian function. Unfortunately, ovarian torsion is difficult to diagnose due to non-specific abdominal symptoms. It is especially difficult to diagnose in pregnancy due to the enlarged uterus which leads to trouble visualizing anatomy as well as similar symptom presentation that occurs in pregnancy.

Case Information

An unusual case of ovarian torsion in the third trimester presented with late onset of abdominal pain and non-reassuring fetal heart tones. The ovarian torsion was unable to be clearly visualized with ultrasound and was found upon emergent Cesarean delivery that was performed due to non-reassuring fetal heart tones. The ovary was found to be necrotic and a right salpingo-oophorectomy was performed.

Conclusion

It is rare for ovarian torsion to occur in pregnancy and even more rare to have an effect on the fetal status as presented in this case. Upon review of the literature, this case was found to be truly unique in the rarity of occurrence of ovarian torsion late in pregnancy, as well as the effect on the fetal status. Only 2 other case reports of intra-abdominal inflammatory conditions in the third trimester were identified to have caused fetal distress, resulting in an emergent Caesarian delivery.

Sponsor: N/A
IRB/IACUC#: 2017-162
High Risk Anal and Cervical HPV Infections among Sexual Minority Women

Purpose: To examine anal and cervical high-risk HPV (hr-HPV) infections among women having sex with women, and women having sex with men and women.

Methods: We conducted a cross-sectional study of women ages 18-70 in treatment at the largest substance use disorders center in North Texas who participated in a cancer prevention program providing well woman exams. Demographics, past trauma, sexual practices, and risky behaviors were collected using self-administered questionnaires. Chi-square tests and adjusted logistic regression controlling for age (AOR) were used to compare hr-HPV infection prevalence rates by sexual minority status.

Results: A total of 757 women with histories of trauma were included in this study; 84% were smokers, 53% self-reported previous incarceration and 25% traded sex for drugs. Nearly one-quarter reported having oral, vaginal, or anal sex with women only, or with men and women. Among this sexual minority group, 40% tested positive for anal hr-HPV vs 34% of heterosexual women ($P=.18$). Cervical hr-HPV was present in 31% of sexual minority women and 27% of heterosexual women ($P=.20$). Sexual minority status was not significantly associated with anal hr-HPV (AOR 1.23 95% CI .85-1.77) or cervical hr-HPV (AOR 1.09 95% CI .76-1.55) compared to heterosexual women. Cervical hr-HPV was significantly associated with anal hr-HPV among both groups ($P$)

Conclusion: These findings inform providers about HPV infections among sexual minority women, and the appropriateness of anal pap and HPV co-testing exams in this population.

Sponsor: N/A
IRB/IACUC#: 2014-012
Marital Status and Cervical Screenings Among a Vulnerable Population

Introduction: The CDC’s Healthy People 2020 goal is that 93% of eligible women receive a cervical cancer screening by 2020. Evidence based strategies for increasing completion rates include doctor recommendation and reminders by telephone and mail. Other strategies such as educating husbands on the importance of cervical cancer screenings for their wives has had success in underserved, vulnerable populations, such as refugees. However, there is little evidence whether these strategies work among women at highest risk of cervical cancer as they move in and out of the criminal justice system and sell sex for mere survival needs. Given the political and social dynamics on the street, we hypothesized that marital status would not have the same positive effect that we observe in the general population or in other underserved populations.

Methods: We performed a cross-sectional analysis on data collected from 1172 women who were in substance abuse treatment at Nexus Recovery Center from 2012–2016 and participated in the CPRIT funded Sound Mind, Sound Body Project. Women who received a well-woman exam through this cancer prevention project and declared a marital status at enrollment (married, divorced, widowed, in a relationship, single) were included in the final study population (n=744). Outcomes assessed were high-risk HPV screening results and STI results. Bivariate analysis was performed using Statistical Analysis Software to calculate chi-square p values ($\alpha < 0.05$), and age-adjusted odds ratios.

Results: Our study population had an average age of 33.4 years; 37% minority race; 26% with less than a high school diploma. Nearly half were currently (n=85) or previously (n=253) married. The odds ratios for cervical HPV and cervical chlamydia were close to the null (AOR=1.02, 95% CI:0.60-1.74; AOR=0.77, 95% CI:0.23-2.56, respectively). Similarly, the association between marriage and anal screenings was also statistically insignificant (anal HPV: AOR=0.69, 95% CI:0.41-1.19; anal chlamydia: AOR=1.20, 95% CI:0.45-3.21).

Conclusion: Marriage did not offer positive benefits in cervical cancer screenings among vulnerable populations with complex needs and addictions. Findings serve to highlight both the need for multi-sector strategies that could ensure adherence to needed cancer screenings and a critical need to inform healthcare providers how self-reported marital status is determined on the street, in order to provide best cancer prevention recommendations.

Sponsor: Cancer Prevention and Research Institute of Texas
IRB/IACUC#: 2014-012
Analysis of Maternal Mortality Review in the United States

Background:
Maternal mortality has been a persistent concern locally, nationally, and globally. The maternal mortality rate in Texas has been rising since 2010 and is one of the worst rates in the U.S. In fact, the Texas rate is almost double that of the U.S. The Texas Maternal Mortality and Severe Morbidity Task Force (MMMTF) was set up within the Department of State Health Services (DSHS) to study and review cases of pregnancy-related causes of maternal mortality and severe morbidity. Other states have conducted similar reviews prior to Texas’ MMMTF. They have seen improvements in maternal mortality from the implementation of their recommendations.

Objective:
To compare and contrast previous maternal mortality and morbidity reviews of other states and determine its impact on the rate of maternal mortality because of the review. The results of these reviews can be used to guide the implementation of appropriate interventions to reduce the rate of maternal morbidity and mortality in Texas.

Methodology:
A review of literature and “grey” literature was conducted. Studies were selected based on the following criteria: state/city review, case definition of maternal mortality, year maternal mortality review was implemented, type of review (only medical records, family interviews, etc.), recommended/implemented interventions, and composition of the taskforce. Inclusion criteria consisted of publication period between 2007 and 2017, search terms “death review” and “maternal mortality”, and reviews within the United States. Exclusion criteria was comprised of countries outside of the U.S., and infant or other mortality reviews.

Results:
The review revealed that a maternal mortality surveillance system helps to identify interventions and recommendations unique to the needs of each State, making it difficult to compare effective practices across regions. However, evidence-based practices that have been successful with populations and infrastructures similar to Texas are worth considering.

Conclusion:
A state level review of maternal death allows in-depth analyses of the problem of maternal mortality. It allows for a richer, more nuanced picture than what would otherwise result from analysis of vital statistics. These conclusions can help establish a surveillance system and also have the potential to give rise to recommendations to address maternal morbidity and mortality.

Sponsor: N/A
IRB/IACUC#: N/A
Current Physical Activity Levels may Not be a Protective Factor for Cognitive Decline in Women Ages 55 to 64

Purpose: Physical activity could help prevent or slow deficits in cognition as an individual age; however, little is known about this relationship in females ages 55 to 64. The purpose of this study was to assess the relationship between physical activity levels and cognitive decline in females ages 55 to 64.

Methods: This cross sectional analysis used 2015 data from the Behavioral Risk Factor Surveillance System (BRFSS) for females ages 55 to 64 in Connecticut, Montana, and Oregon. Logistic regression was used to assess the relationship between physical activity levels and cognitive decline while controlling for health and demographic factors.

Results: Across states, few participants reported cognitive decline (10-14%), and only one-fifth reported being inactive (18-29%), while twice as many reported being highly active (34-48%). Adjusted results indicated that cognitive decline was not found to be significantly related to physical activity levels in any state, but cognitive decline was significantly related to number of health conditions, mental health, and substance use (all with moderate to large effect sizes) in two or three of three states.

Conclusion: Across states, cognitive decline was not related to physical activity levels in females ages 55 to 64. The measurement for cognitive decline provided a limited scope of the condition and this study was unable to control for menopause and hormone replacement therapy, which may affect the outcome.

Primary providers should not screen for physical activity levels related to cognitive decline in this population, but should screen for cognitive decline, multiple health conditions, current mental health issues, and substance use, if symptoms present for any of these in this target population.

Providers should educate patients about the overall benefits of physical activity, but should focus on concurrently managing health conditions and discontinuing tobacco use as related to cognitive decline in females ages 55 to 64.

Sponsor: N/A
IRB/IACUC#: 2017-070
Survival sex, drug use, and reproductive autonomy: a study of hysterectomy rates among high-risk reproductive aged women.

Purpose: Marginalized and high-risk groups often present with health outcomes that differ from the general population. The aim of the current study was to compare hysterectomy rates in a large sample of reproductive aged truck stop and street sex workers with the general population, and to explore the social and medical variables underlying this difference.

Methods: Using a multi-sector community partnership with law enforcement, we accessed hard to reach, migratory truck stop and street sex workers moving through transportation corridors. Unique to this partnership was provision of immediate resources directly on the street and a safe exit strategy. Women choosing to exit were immediately diverted to treatment services with long-term wraparound services. In a follow-up cancer prevention study, we collected survey and clinical data from 1167 women aged 18-78 years at Nexus Recovery Center in Texas (2014-2016). Hysterectomy status was collected by self-report and confirmed by clinical examination.

Results: Of the 1167 women participating in the study, 67% reported physical and sexual trauma, 55% prior incarceration, 28% traded sex for drugs, and 34% self-identified as minority race. Of the 81 (6.9%) hysterectomies, 48 (60%) occurred among women from 25-44 years, of whom 3 (6%) were never pregnant. There was no association between race and hysterectomy status (OR=0.80, 95% CI= 0.49-1.30).

Conclusions: Women with complex trauma histories, co-occurring disorders, and history of trading sex for survival needs had higher hysterectomy rates than the general population (3%). The high prevalence of hysterectomy among reproductive aged women has significant implications for reproductive autonomy, and may be indicative of limited access to information about medical procedures and alternatives. Communication with healthcare professionals may be hindered by stigmatization. These marginalized groups are present globally, many hidden in plain sight. This multi-sector street based initiative has been replicated in other settings and casts a wide net to also reach trafficked women with trauma-informed care.

Sponsor: N/A
IRB/IACUC#: 2014-012
For CAD, Does Mental Health Differ by Ethnicity/Race in Post-MI Females 50 Years and Older?

Purpose: Older males and females have similar incidence of coronary artery disease (CAD); however, there is limited research surrounding how mental health in post-myocardial infarction (MI) patients differs by ethnicity. Therefore, the purpose of this study was to determine whether mental health differs by ethnicity in post-MI older adult females with CAD.

Methods: This cross-sectional analysis used 2015 BRFSS data for females 50 years of age and older from Arkansas, Kentucky, and Tennessee. Multiple logistic regression analysis was used to assess the relationship between mental health and ethnicity/race while controlling for age, education level, income level, marital status, physical activity, and depression.

Results: The majority of women reported 30 good days of mental health in the last month (56-58%); and 73-80% reported their race as white. After controlling for demographic factors, physical activity and depression, mental health did not differ significantly by ethnicity/race in any of the three states. However, mental health was significantly related to age in two of three states and depression across all states.

Conclusion: Mental health did not differ significantly by ethnicity in post-MI older adult females with CAD. However, within this target population, good mental health was significantly related to those aged 65 and older and to those with a previous diagnosis of depression. Although there was no information regarding mental health progression following a myocardial infarction, primary care providers and cardiologists should screen all post-MI female patients, despite their ethnicity, for poor mental health, especially those who are aged 50-64 or who have a previous diagnosis of depression. Mental health education and a referral to a mental health professional, as necessary, should be provided to post-MI older adult females of all ethnicities.

Sponsor: N/A
IRB/IACUC#: 2017-070
Protective Potential of Hormone Replacement Therapy in Post-Menopausal Women

Purpose:
Menopause is the cessation of a woman’s menstrual cycle, generally diagnosed after 12 months of amenorrhea. Due to hormonal changes, women often undergo physical and behavioral changes: including hot flashes, mood lability, and sleep disturbances. The first line of treatment for menopausal symptoms is hormonal replacement therapy (HRT). HRT use does have risks, such as cardiovascular disease and breast cancer. Younger postmenopausal women had reduced risks compared to older postmenopausal women. Aging is linked with oxidative stress (OS), and thus OS may be a mediating factor in HRT risk. Previously, we showed HRT given prior to OS insult is neuroprotective. If given after OS insult, HRT is neurotoxic in dopaminergic neurons. Therefore, we will determine if OS and HRT interactions is a general phenomenon applicable to all cell types or specific to neurons. Further, we will determine if either the estrogen receptor or the androgen receptor mediate OS and HRT interactions.

Materials and Methods:
We utilized 1RB3AN27 (N27) neuronal cells derived from female fetal mesencephalic tissue, human embryonic kidney cells (HEK), and C6 glial cells. Cells were grown in their preferred media supplemented with L-glutamine, penicillin-streptomycin and fetal bovine serum. Prior to experimentation, media was switched to charcoal stripped serum to remove hormones. To model post-menopause, hormone-deficient cells were exposed to OS using hydrogen peroxide (H2O2). Three different HRTs were examined: testosterone, 17-beta estradiol, and membrane impermeable dihydrotestosterone (DHT-BSA). An estrogen receptor inhibitor (ICI-182,780) and androgen receptor degrader will be included to explore the hormonal pathways. Cell viability was assessed with MTT assays.

Results:
Testosterone, estradiol, and DHT-BSA had different effects, which were dependent on the presence of OS. Both testosterone and estradiol were protective when given prior to OS, but DHT-BSA was not protective. Conversely, all HRTs given after OS exacerbated OS-induced cell loss.

Conclusion:
Based on our results, HRT's protective effects against subsequent OS damage is predominantly due to estrogen hormonal pathways. Activation of androgen pathways may not be neuroprotective and could be damaging. Currently, post-menopausal women are mainly using estradiol-based HRT. However, an increasing trend for off-label use of testosterone-based HRTs has been noted in post-menopausal women to improve libido.

Sponsor: NIH RO1 Grant
IRB/IACUC#: N/A
For General Health, does General, Mental, and Physical Health differ by Healthcare Access for Middle-aged Females?

Introduction: General health and healthcare access, defined as coverage and cost, have been shown to be related in previous research, but these studies did not focus on middle-aged females (1). Therefore, the purpose of this study was to determine whether general, mental, and physical health differed by healthcare access in middle-aged females.

Methods: This cross-sectional analysis used 2015 BRFSSS data for middle-aged females aged 35-54 from Alabama, Arkansas, Louisiana, and Mississippi. Multiple logistic regression analysis assessed the relationship separately for good general health, good mental health, and good physical health with healthcare access (coverage and cost) while controlling for routine checkup, high cholesterol, age, ethnicity/race, education, income, metropolitan status, and veteran status.

Results: For females aged 35-54, the majority of participants reported having good general health (73-79%), mental health (54-58%), and physical health (54-59%). Most participants reported having healthcare coverage (82-92%), and that cost did not preclude them from provider visits in the past year (74-82%). The results of adjusted analysis indicated:

- Healthcare cost (moderate to large effect sizes) related to good general and physical health in three of four states.
- High cholesterol (moderate to large effect sizes) related to good general, mental, and physical health in three of four states.
- Income level of over $25,000 (moderate to large effect sizes) related to good general, mental, and physical health in three of four states.

Conclusion: Overall, good general health and physical health were related to healthcare cost while healthcare coverage was not significant for good general, mental, or physical health in any state. The results of this study may generalize to middle-aged female patients in primary care practice. Limitations to this study include a lack of information on the extent of cost as a barrier. Healthcare services should consider a patient’s ability to manage costs of treatment, medications, and chronic health management.

Sponsor: N/A
IRB/IACUC#: 2017-070
Oral Presentations
Cancer (Abstracts in the 300s)

326 - Oral

Classification: GSBS Student
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**Cell surface PCNA is a marker of pancreatic and colon cancer stem cells and inhibits NK cell effector function.**

Purpose: Cancer stem cells (CSC), a unique subset of tumor cells, possess a stem-cell-like phenotype and are thought to facilitate metastasis by escaping NK cell effector function. There are numerous markers used to identify CSC; of which include surface markers CD44 and CD133, and transcription factors NANOG, SOX2, and Oct-4. NK cells participate in the innate immune response against cancer without prior sensitization. NK cell function depends on a balance of signals transmitted from activating and inhibitory receptors interacting with ligands on the surface of target cells. Cancer cells may evade NK-mediated killing by expressing or secreting ligands for NK cell inhibitory receptors. NKP44 can function as an activating receptor that induces NK cell cytotoxicity or an inhibitory receptor depending on ligand interaction. Proliferating cell nuclear antigen (PCNA) associates with Human Leukocyte Antigen I (HLA I) and forms the inhibitory ligand for NKP44, resulting in the inhibition of NK function. We hypothesize surface PCNA is a marker for CSC in pancreatic and colon cancer.

Methods: Pancreatic (Panc-1) and colon (HCT 116) cancer cells were labeled with antibodies against PCNA, CD44, and CD133 and flow cytometry was performed to determine surface expression. Cells were labeled and sorted for cell surface PCNA expression via fluorescence activated cell sorting; NANOG, SOX2, and Oct-4 were analyzed by qRT-PCR from sorted cells. NK receptor-ligand interactions were blocked by incubating cells with anti-PCNA or control antibodies and a chromium release killing assay was performed.

Results: In both Panc-1 and HCT 116 cells, a PCNA*CD44*CD133* population was detected. Furthermore, cell sorting and qRT-PCR confirmed cells with cell surface PCNA have increased expression of CSC transcription factors compared to PCNA- cells. Blocking the interaction of NKP44 and PCNA enhanced the specific lysis of cells by primary NK cells.

Conclusions: Cell surface PCNA is associated with co-expression of CD44 and CD133 as well as increased CSC transcription factor expression. Collectively these data demonstrate that surface PCNA is a marker of pancreatic and colon CSC. Additionally, cell surface PCNA on CSC facilitate escape from NK cell killing by interacting with NKP44 and transmission of an inhibitory signal. Our research implicates that blocking NKP44-PCNA interaction may provide novel immunotherapeutic targets for pancreatic and colon cancer stem cells and prevent metastasis.

Sponsor: NIH NS101481
IRB/IACUC#: 2008-094
THE IMPACT OF ACUTE CENTRAL HYPOVOLEMIA ON CEREBRAL HEMODYNAMICS: DOES SEX MATTER?

Trauma-induced hemorrhage is a leading cause of disability and death due, in part, to impaired perfusion and oxygenation of the brain. While cerebrovascular function is known to differ between males and females, it is not clear if cerebrovascular responses to blood loss are differentiated based on sex. Purpose: To examine the effect of sex on cerebral blood velocity and oxygenation responses following simulated hemorrhage induced via application of lower body negative pressure (LBNP) to presyncope. Methods: Healthy males (n=11, 25±1 yr) and females (n=7, 27±1 yr) participated in a LBNP ramp protocol (-3 mmHg/min) until presyncope. Middle cerebral artery velocity (MCAv), cerebral oxygen saturation (ScO2), end-tidal CO2 (etCO2), heart rate (HR), arterial pressure (MAP) and stroke volume (SV) were measured continuously. Results: Baseline MCAv was higher in females vs. males (70.3±5.8 vs. 57.8 ± 2.1 cm/s, p=0.03), despite a lower etCO2 (37.9±0.9 vs. 44.4±1.5 mmHg, p=0.02). While LBNP tolerance was higher for males compared with females (1675.5±123.1 vs. 1315.9±140.0 s; p=0.08), the absolute and relative (% change) increases in HR and decreases in MCAv, MAP, SV, and etCO2 were similar between males and females at presyncope (p≥0.11). Males exhibited a lower rate of change in MCAv over LBNP time (-0.56±0.10 vs. -0.92±0.09 cm/s/min, p=0.03) and a greater maximum decrease in ScO2 (-7.6±1.3 vs -5.3±0.9 %, p=0.08) when compared with females, most likely due to the higher tolerance in this group. Conclusions: These findings suggest that sex may influence the cerebral hemodynamic responses to simulated blood loss in young healthy adults.

Sponsor: US Army MRMC
IRB/IACUC#: 2012-163
Extracellular Superoxide Dismutase Hinders Effective Containment of Listeria monocytogenes by Neutrophils

Purpose: Increased activity of Extracellular Superoxide Dismutase (ecSOD), an enzyme widely regarded as having protective functions during ROS induced inflammation, has been shown to be detrimental to host survival during infection with the intracellular bacteria, Listeria monocytogenes (Lm). Although, we have also demonstrated that neutrophils are essential for protection during Lm infection, a higher percentage of neutrophils are present in mice with high ecSOD activity during Lm infection. However, these mice are still more susceptible to infection in comparison to mice that lack ecSOD activity. These paradoxical findings led to the objective to better understand how ecSOD activity modulates the protective functions of neutrophils during Lm infection.

Materials and Methods: For these studies, ecSOD congenic mice: ecSOD HI mice with high ecSOD activity, ecSOD WT mice with normal ecSOD activity, and ecSOD KO mice with no ecSOD activity were utilized. To determine phagosomal containment, we made use of flow cytometry and a strain of Lm, actA:LMGFP, which only fluoresces GFP when the bacteria escapes out of the phagosome into the cytosol.

Results: A higher percentage of neutrophils from the ecSOD KO mice took up Lm in comparison to the HI neutrophils. Correlated with this was also a higher percentage of ecSOD KO neutrophils allowing for phagosomal escape in comparison to the ecSOD HI neutrophils. Analysis of the mean fluorescence intensity (MFI) showed that although there were more bacteria present in the ecSOD KO neutrophils, the amount of escaped bacteria was comparable to that in the ecSOD HI neutrophils. Treatment of the ecSOD KO neutrophils with IFN-g, an activator of neutrophils, also led to better phagosomal containment. Though the IFN-g treated neutrophils took up more bacteria, there was no difference in the amount of escaped bacteria in comparison to the non-treated cells.

Conclusion: EcSOD activity hinders the ability of neutrophils to keep Lm contained in the phagosome which prevents effective bacterial killing. Additionally, neutrophil activation with IFN-g also makes the cells more effective at bacterial containment. However, the effect of ecSOD activity in conjunction with IFN-g is yet to be determined. Future studies on how ecSOD affects bacterial killing and other functions downstream of phagosomal escape will aid in a better understanding of how ROS can modulate neutrophil function during intracellular bacterial infections.
Atrophied thymus can serve as a tumor reservoir for harboring melanoma cells

Purpose: Tumor metastatic relapse is responsible for main cancer associated mortality and potentially arises from the undetectable minimal number of tumor cells, which are able to resist radio-chemotherapy at a dormant state hiding in certain organs (termed: tumor reservoirs). The largest T-lymphoid organ, the thymus, has been suggested as this kind of pre-metastatic tumor reservoir for B-lymphoma cells. It remains unknown whether the thymus is able to harbor non-lymphoid solid tumor cells, why chemotherapy cannot thoroughly eliminate cancer cells in the thymus, and what the state of thymic occult cancer cells is during chemotherapy.

Methods: With melanoma inoculated and genotoxic doxorubicin (Doxo) treated mouse model, we determined that the thymus, particularly the atrophied thymus, was able to harbor blood stream-circulating melanoma cells. Using specific in vivo + in vitro technique, where thymuses of doxorubicin- or PBS-treated mice are co-cultured with doxorubicin-treated melanoma cells in trans-well system we want to provide the insight of the changes in the status of cancer cells.

Results: We found that chemotherapy-resulted DNA-damage response triggered p53 activation in non-malignant thymic cells, which in turn resulted in thymocyte death and thymic epithelial cell senescence to develop an inflammatory thymic microenvironment. Co-culture of PBS- or Doxo- treated thymus with Doxo-treated melanoma cells provides evidence that chemotherapy-altered inflammatory thymic microenvironment protects cancer cells from apoptosis via induction of dormancy.

Conclusion: Therefore, the thymus, which becomes a pre-metastatic reservoir for non-lymphoid solid tumor cells under chemotherapy, should be a novel target in antitumor therapy for considering and preventing from tumor metastatic relapse.

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Oxidative Stress During Simulated Hemorrhage Elicited by Lower Body Negative Pressure

Purpose: Hemorrhage is a leading cause of potentially preventable death in both civilian and military trauma settings. Hemorrhage also elicits an oxidative stress response as a direct result of losing blood volume, or as an indirect response to ischemia-reperfusion injury. Lower body negative pressure (LBNP) is a well validated, non-invasive, and reproducible approach to simulate hemorrhage by inducing central hypovolemia in healthy conscious humans. The oxidative stress response to simulated hemorrhage via LBNP has not been quantified. We hypothesized that systemic markers of oxidative stress would increase with application of LBNP.

Methods: 15 healthy human subjects (11M, 4F; 27 ± 1 y) were recruited for a step-wise LBNP exposure to presyncope (systolic blood pressuresymptoms). After baseline, LBNP pressure progressively decreased every 5 minutes to -15, -30, -45, -60, -70, -80, -90, and -100 mmHg. Arterial pressure and stroke volume were measured continuously via finger photoplethysmography, and venous blood samples were collected at baseline and during the LBNP profile. Plasma samples were analyzed for F2-isoprostanes, a global marker of oxidative stress, via gas chromatography/mass spectrometry.

Results: The magnitude of central hypovolemia, indexed by the % change in stroke volume, ranged from a 27% to 74%. LBNP induced a -12.6 ± 2.6 % decrease in MAP (%Δ MAP) from baseline (P

Conclusion: Simulated hemorrhage elicited by step-wise LBNP to presyncope elicited an increase in a global marker of oxidative stress. These findings have important implications in the study of hemorrhage and potential application of targeted interventions.

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Life on the Catwalk – Age and redox state effects on mouse gait

1. Purpose

Human clinical research has determined that changes in gait speed can be predictive of other impairments and can help identify at-risk individuals for further declines. However, age-related gait changes are not well defined in rodents, even though they are used as the primary pre-clinical model for a multitude of diseases and for aging research. The purpose of our study was to measure age-related differences in gait, using an automated system, the CatWalk™ XT. Furthermore, age-related functional declines have been associated with a decrease in the reduced to oxidized glutathione ratio leading to a pro-oxidizing cellular shift. Using a model of chronic glutathione deficiency, we sought to determine whether redox state was a key factor in age-related gait impairments. Our hypothesis was that gait declines observed with aging would be exacerbated in glutathione-depleted mice.

2. Methods

Groups of wild-type (gclm+/+) and knock-out (gclm-/-) mice aged 4, 10 and 17 months were tested on the CatWalk and gait measurements were recorded. Resulting dependent measures including gait speed, front and hind base of support, front and hind stride length, front and hind stride speed, front and hind step cycle, and front and hind duty cycle were analyzed using two-way analyses of variance with Age and Genotype as between-groups factors, followed by pairwise comparisons.

3. Results

Age-related declines were observed in all aforementioned measures of gait, and chronic glutathione depletion was unexpectedly associated with delays in age-related declines for some of the measures.

4. Conclusions

The CatWalk is a useful and sensitive tool to assess gait changes with age in rodents, and further studies will be required to identify the potential compensating mechanisms underlying the effects observed with the chronic glutathione depletion.

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let-7i Inhibition Potentiates Progesterone-Induced Functional Recovery in a Mouse Model of Ischemia

Background: Progesterone (P4) is a potent neuroprotectant and a promising therapeutic for stroke treatment. However, the underlying mechanism(s) remain unclear. One known mediator of P4’s protective function is brain-derived-neurotrophic-factor (BDNF). Of note, we recently reported that P4 induces a significant release of BDNF from primary astrocytes, through progesterone-receptor-membrane-component-1 (Pgrmc1). This receptor is abundantly expressed in the brain and mediates various beneficial effects of P4 including anti-apoptosis spinogenesis, and BDNF release. What is not known, however, is how the expression of this receptor is regulated.

Purpose: This study was aimed to elucidate what regulates the expression of Pgrmc1 and BDNF in glia and how such regulation influences the neuroprotective function of P4 in the ischemic brain. We hypothesized that let-7i represses P4’s neuroprotective effects by down-regulating the expression of both Pgrmc1 and BDNF in glia, leading to: 1) suppression of P4-induced BDNF release from glia, and 2) attenuation of the beneficial effects of P4 on neuronal survival and markers of synaptogenesis in the ischemic brain.

Methods: Primary cortical astrocytes and neurons were used as experimental models to investigate the role of let-7i in P4’s action in vitro. For in vivo experiments, we induced stroke using the middle cerebral artery occlusion (MCAo) method in ovariectomized mice (a model of surgical menopause). Let-7i expression was manipulated using a let-7i inhibitor, delivered via intracerebroventricular (ICV) injection.

Results: Our data suggest that the microRNA (miRNA), let-7i, is a negative regulator of Pgrmc1 and BDNF in glia, and that let-7i disrupts P4-induced BDNF release and P4’s beneficial effects on cell viability and markers of synaptogenesis. Results from our in vivo experiments revealed that inhibiting let-7i enhances P4 induced neuroprotection and facilitates functional recovery following stroke.

Conclusions: Collectively, the data presented here suggested that in the ischemic brain, let-7i negatively influences P4-induced neuroprotection via regulation of the Pgrmc1/BDNF axis. As such, inhibition of let-7i may be an effective means to enhance the efficacy of P4 in treating ischemic stroke. In addition, the discovery of such factors that regulate the cytoprotective effects of P4 may lead to the development of biomarkers to differentiate/predict those likely to respond favorably to P4 versus those that do not.

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Corticotropin-Releasing Hormone Receptor 2 in the Nucleus of the Solitary Tract Contributes to Sleep Apnea Induced Hypertension

Purpose: This study tested the hypothesis that corticotropin-releasing hormone (CRH) derived from the paraventricular nucleus of the hypothalamus (PVN) acts in the nucleus of the solitary tract (NTS) to facilitate sleep apnea induced hypertension.

Materials and Methods: To model sleep apnea induced hypertension, we exposed rats to intermittent hypoxia (IH) for 7 days. To detect CRH type 1 and type 2 receptors (CRHR1 and CRHR2) in the NTS, we conducted in situ hybridization. To study the signaling pathway of CRH, we performed calcium imaging on NTS slice preparation using Fura-2-acetoxymethyl ester. To test whether central CRH contributes to IH-induced hypertension, we implanted telemetry transmitters and osmotic mini pumps to infuse CRH receptor agonist/antagonist into the 4th ventricle of rats. To selectively excite CRH-producing pathways from the PVN to the NTS, we optogenetically stimulated the PVN and the NTS of CRH-Cre mice that received intra-PVN injections of Cre-inducible viral constructs expressing Channelrhodopsin 2 (ChR2).

Results: The mRNA level of CRHR2 was significantly higher than CRHR1 in the NTS. CRH induced a transient increase of intracellular calcium level in NTS neurons that was abolished by the voltage-dependent calcium channel blocker nifedipine. CRH-induced calcium influx was attenuated by the CRHR2 antagonist K41498 but not by NBI-35965, an antagonist for CRHR1. Calcium influx was induced by the CRHR2 agonist Urocortin II but not by the CRHR1 agonist Stressin I. More importantly, IH decreased the CRHR2 mRNA level and attenuated the CRH-induced calcium influx in the NTS. Further in vivo studies revealed that IH-induced hypertension was significantly attenuated by chronic intra-4th ventricle infusion of the CRHR2 antagonist K41498, but was significantly exacerbated by chronic intra-4th ventricle infusion of the CRHR2 agonist Urocortin II. Optogenetic stimulation of either CRH somas in the PVN or CRH fibers in the NTS that originated from the PVN significantly increased blood pressure (somas, 12.3 ± 1.13 mmHg; fibers, 3.54 ± 0.69 mmHg), suggesting that activation of CRH projections from the PVN to the NTS increases blood pressure.

Conclusions: These results suggest that CRH derived from the PVN activates CRHR2 in the NTS, which may contribute to sleep apnea induced hypertension; down-regulation of CRHR2 and CRHR2-mediated calcium influx in the NTS may serve as compensatory responses to protect against sleep apnea induced hypertension.

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Pregnancy Augments the Vasoactive, Metabolic, and Inflammatory Functions of Uterine Perivascular Adipose Tissue

Introduction: Perivascular adipose tissue (PVAT) is functionally different from other adipose depots and has vasoactive effects that vary with anatomic location and disease state. Healthy pregnancy involves remodeling of the vessels that supply blood flow to the uteroplacental unit (i.e. uterine arteries) and increases adipose tissue metabolic and inflammatory functions. The main objective of this study was to examine whether pregnancy changes the function of PVAT surrounding the uterine arteries (utPVAT).

Hypothesis: Healthy pregnancy augments the vasoactive, metabolic, and inflammatory functions of utPVAT.

Methods: Pregnant (gestational day 16, term=22-23 days) and aged-matched non-pregnant rats were used. To evaluate the effects of utPVAT on endothelium-dependent dilation in uterine artery, we performed concentration-response curves to acetylcholine (ACh) in the presence or absence of utPVAT using wire myography. A proteome adipokine profiler and reverse transcription polymerase chain reaction (RT-PCR) were used to assess protein and gene expression of utPVAT adipocytokines, respectively.

Results: Incubation of uterine arteries from pregnant rats with utPVAT reduced ACh-induced relaxation responses following constriction with 60 mM potassium chloride solution [\( pEC_{50} \), +PVAT (n=5): 6.25 ± 0.12 vs. –PVAT (n=5): 6.66 ± 0.18, \( p = 0.02 \) or \( 10^{-6} \) M phenylephrine [\( pEC_{50} \), +PVAT (n=9): 6.86 ± 0.10 vs. –PVAT (n=9): 7.61 ± 0.17, \( p=0.0004 \)]. This effect was not seen in arteries from non-pregnant animals. Uterine PVAT from pregnant rats (n=3) had reduced mRNA expression of peroxisome proliferator-activated receptor gamma (PPAR-\( \gamma \)) by 5.7 fold compared to utPVAT from non-pregnant rats (n=4). Leptin mRNA expression was reduced by 6.4 fold and protein expression was increased in utPVAT from pregnant rats compared to utPVAT from non-pregnant rats. Interleukin (IL)-10, IL-6, and monocyte chemoattractant protein (MCP)-1 mRNA expression in utPVAT did not differ between groups but protein expression of these adipocytokines was increased in utPVAT from pregnant rats.

Conclusion: In pregnancy, utPVAT reduces endothelium-dependent relaxation in uterine arteries. In addition, pregnancy regulates metabolic and inflammatory adipocytokines in utPVAT at the level of protein translation. Future studies will determine the functional role of the vasoactive and molecular changes in utPVAT and their impact on uterine blood flow and fetal growth.

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